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The Journal of the British Paediatric Association

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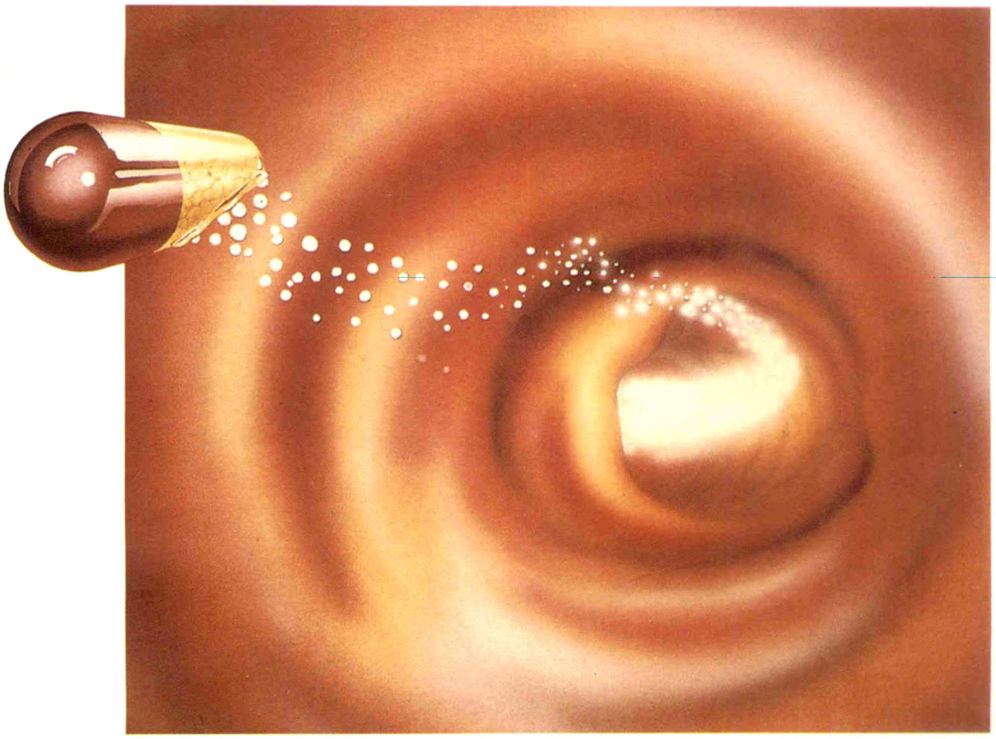

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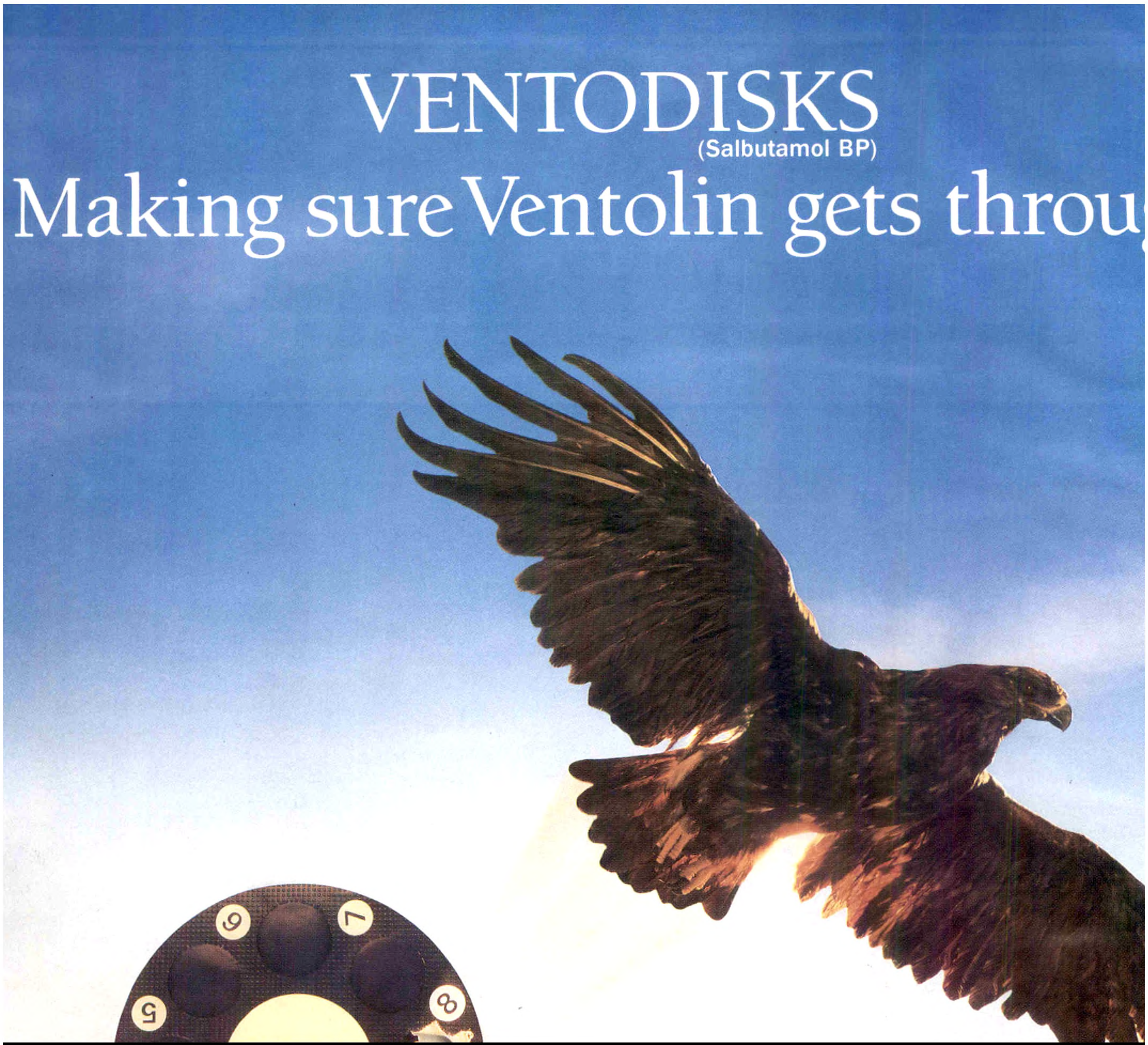
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Archives of Disease in Childhood 1991; **66:** 81–84

ARCHIVES OF
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The Journal of the British Paediatric Association

Annotations

Respiratory rate and pneumonia in infancy

The World Health Organisation (WHO) programme to control acute respiratory infections uses simple clinical signs to identify pneumonia, to assess its severity and whether there is a need for hospitalisation, and to decide on the type of antibiotic treatment. The clinical signs must be appropriate for community health workers, nurses, and physicians in both outpatient and hospital settings. The clinical signs include cyanosis, inability to feed, subcostal retractions, wheezing, and respiratory rate thresholds. The respiratory rate (breaths per minute) thresholds are set at 60 for infants less than 2 months of age, 50 for infants from 2 to 12 months, and 40 for children aged 1 to 5 years. WHO recommends a repeat respiratory rate count for infants under 2 months of age when the initial count is 60 or higher.

Acute respiratory infection during early infancy presents a special challenge with respect to both assessment and management. Young infants have less specific clinical syndromes so that the clinical presentation of pneumonia is often similar to that of sepsis, meningitis, or a urinary tract infection. Non-specific signs such as inability to feed, fever, hypothermia, difficulty awakening, and convulsions were added in special WHO guidelines for the infant under 2 months. This new approach reflects the finding that acute respiratory infection has the highest incidence and mortality in young infants. Twenty to 30% of the total acute respiratory infection related childhood (under 5 years of age) mortality occurs in infants under 2 months of age.[1]

The usefulness of respiratory rate thresholds to identify pneumonia is a critical aspect of the programme. Several factors other than age and presence of a lower respiratory infection will affect the respiratory rate and its variability. These involve the method of counting (observation, auscultation, monitor), duration of counting interval, state of the child (awake, sleeping, feeding, and calm or agitated) and gender, as well as associated non-respiratory conditions such as fever, acidosis, dehydration, and malnutrition. There may also be differences between infant baseline respiratory rates and variability in infants living in developing and developed countries related to differences in low birth weight, nutrition, activity levels, genetic and other factors.

The recent article by Morley *et al* entitled 'Respiratory rate and severity of illness in babies under 6 months of age' sought to define the normal range of respiratory rate and assess the usefulness of a threshold respiratory rate of 50 to identify lower respiratory infection.[2] In reviewing other published studies that describe the normal range of infant respiratory rates, a major methodological difference becomes apparent. Other published studies determined the mean respiratory rate in a relatively small number of infants over a prolonged period of time with continuous electronic monitoring while Morley *et al* determined the mean respiratory rate of a large number of infants during a very short period of time: three 15 second intervals. The study of Morley *et al* found overall a mean (SD) respiratory rate for awake infants seen in the hospital or home of 61 (18) and 61 (14) and 42 (12) for sleeping infants. Mean respiratory rates for each month of life were similar: 57, 57, 61, 63, 59, and 59 respectively.

Determination of normal range of respiratory rate by electronic monitoring

Studies using continuous electronic monitoring for prolonged time periods are reviewed in table 1.[3–6] Mean respiratory rates (SD) are shown by the state of the infant (awake, active sleep, quiet sleep, and all states) and age. Studies using this method report a lower range of baseline mean respiratory rates for both awake and asleep infants. In contrast to Morley *et al*, each study also documented a decrease in mean respiratory rate with age. Hoppenbrouwers *et al* have also reported a lower mean respiratory rate of 4·7 to 5·9 in infant girls compared with boys.[7] Although the numbers in the cited studies using electronic monitoring are small, their findings are supported by work published by Valman *et al*, who used a mean respiratory rate ≥60 persisting for longer than one hour determined by electronic monitoring as a screen in newborns for sepsis or pneumonia.[8] Only 29 (1%) of 2789 infants screened had a respiratory rate ≥60.

Determination of normal range of respiratory rate by observation

An ongoing (unpublished) community based study with twice weekly home visits in Lima, Peru, counted the respiratory rate by observation for 60 seconds in all infants aged less than 3 months and 3 months or older with a history of cough (C Lanata, personal communication). Table 2 shows the results of counts obtained in infants less than 12 months according to the infant's state. The age interval is up to but not including the next month. The mean counts are similar to data obtained by continuous monitoring. Differences between the data obtained by Lanata in Peru and by Morley

Table 1 Mean respiratory rate according to the infant state in studies using continuous electronic monitoring (time interval)

State of infant	*Hoppenbrouwers et al[3] (12 hours)*		*Curzi-Dascalova et al[4] (one sleep cycle)*		*Ashton et al[5] (3 hours)*		*Richards et al[6] (22 hours)*	
	No of subjects	*Mean (SD) respiratory rate*	*No of subjects*	*Mean (SD) respiratory rate*	*No of subjects*	*Mean (SD) respiratory rate*	*No of subjects*	*Mean (SD) respiratory rate*
Awake:								
1 week	8	50 (10)						
1 month	8	48 (6)						
2 months	8	48 (7)						
3 months	8	41 (8)						
4 months	8	40 (9)						
5 months		NA						
6 months	8	43 (10)						
Active sleep:								
1 week	8	51 (8)	22	48 (9)	22	47 (9) to 54 (11)		
1 month	8	42 (6)	11	64 (14)				
2 months	8	36 (6)	14	57 (16)				
3 months	8	31 (3)						
4 months	8	30 (3)	10	43 (10)				
5 months		NA						
6 months	8	28 (4)						
Quiet sleep:								
1 week	8	38 (9)	22	36 (7)	22	43 (13) to 45 (10)		
1 month	8	34 (4)	11	50 (11)				
2 months	8	30 (5)	14	46 (11)				
3 months	8	25 (3)						
4 months	8	26 (3)	10	38 (10)				
5 months		NA						
6 months	8	24 (4)						
Awake and sleep:								
1 week							36	43 (16)
1 month							41	39 (6)
2 months							50	37 (6)
3 months							97	31 (6)
4 months								
5 months							91	27 (4)
6 months								

NA, not available.

Table 2 Mean respiratory rate (per minute) observed at first measurement by age in all infants under 6 months of age and in infants 6–11 months of age with reported cough in Canto Grande, Lima, Peru (January–June 1989)

State of infant	*Age (months)*						
	0	*1*	*2*	*3*	*4*	*5*	*6–11*
Sleeping:							
No of examinations	542	868	852	169	126	109	359
Mean rate	46·18	43·12	41·34	38·88	36·56	36·85	34·38
SD	9·14	7·21	7·47	7·07	7·87	8·28	7·09
Breastfeeding:							
No of examinations	253	671	696	141	115	91	328
Mean rate	50·36	48·98	47·55	45·07	44·69	42·84	40·82
SD	7·77	7·04	7·13	6·78	7·09	6·52	5·83
Awake and calm:							
No of examinations	264	897	1373	467	491	410	2249
Mean rate	49·56	48·33	47·82	44·74	43·76	43·65	40·89
SD	9·51	6·96	6·62	7·07	6·09	6·36	5·34
Awake and not calm but not crying:							
No of cases	17	46	74	44	32	24	220
Mean rate	46·79	50·67	48·11	44·67	44·21	44·56	41·26
SD	9·24	11·41	8·89	10·09	5·71	6·94	6·32

et al in Australia/Great Britain may reflect their respective populations and/or the different methods used to count respirations. The respiratory rate in the Peru study was counted by observing abdominal and chest wall movements for 60 seconds with an electronic timer, but in Australia/Great Britain counts were made with a stethoscope or hand on the abdomen for 15 seconds. The electronic timer allows the field worker to count the rate without needing to watch a timer during the same period. Work in Denver, Colorado, suggests that counting respirations with a stethoscope is similar to counting with an electronic monitor and results in slightly higher mean counts than when observing (EAF Simoes *et al*, personal communication). Simultaneously obtained observed and monitored counts in 101 infants and children found mean monitored counts to be 2–3 breaths/minute higher than mean observed counts. The monitor and stethoscope appear to pick up small breaths that are not appreciated when observing for chest/abdominal movement. After reviewing the paper of Morley *et al*, we compared three 15 second counts obtained by auscultation with counts obtained by observation by two investigators at the same time in 10 infants. The counts obtained by auscultation were an average of 14 breaths per minute higher than those obtained by observing abdominal and chest wall movement. It is also possible that touching an infant with a stethoscope or hand may cause an increased level of agitation that increases the respiratory rate. Counting for 15 seconds rather than 60 seconds may also result in a slightly raised respiratory rate. In Denver, 30 second counts obtained immediately before and after a 60 second count were analysed for infants less than 2 months. Doubling of a 30 second count obtained by observation or monitoring results in a higher mean count of 2–4 breaths per minute compared with the 60 second count. Counting for a 15 second period may further increase this difference. The method of counting may account for the high mean rates and variability reported by Morley *et al*.

Usefulness of respiratory rate thresholds to predict pneumonia

The second aim of the study of Morley *et al* was to assess the usefulness of respiratory rate thresholds to identify children with severe illness or pneumonia. Studies assessing the usefulness of respiratory rate thresholds should clearly define the criteria for acute lower respiratory infection, preferably using radiography findings, the method of counting respira-

infection indicates that a repeat count 45 to 60 minutes later will be less than the threshold in more than two thirds of the patients with an upper respiratory infection in contrast to patients with lower respiratory infection who will usually maintain a raised respiratory rate (EAF Simoes *et al*, personal communication). This observation is supported by field trials in Lima, Peru of respiratory rates counted in neonates during twice a week home visits. Approximately half of the counts above 60 were below 60 when retaken several minutes later.[11]

Although respiratory rate is a useful predictor of lower respiratory infection in young infants, it does not correlate well with hypoxia.[9] The presence of subcostal retractions is

[redacted]

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Archives of Disease in Childhood 1991; **66:** 85–87

Tests for growth hormone secretion

The pattern of growth in childhood is well known to paediatricians: the rapid and rapidly decelerating growth from the third trimester to the second year of life gives way to the steady and slowly decelerating growth of middle childhood (with the mid childhood growth spurt between ages 6 and 8), and the adolescent growth spurt. Possibly less well known is the mathematical division of these phases of growth into infancy, childhood, and puberty components,[1] which correspond to three major control mechanisms.

Growth during fetal life and the first postnatal year is dependent on nutrition. Children born of low birth weight or starved in the first year of life fail to grow at an adequate rate and, if this continues for any length of time, incur a growth deficit which is irrecoverable. Children overfed in utero (infants of diabetic mothers) or shortly after birth become not only fat but also large.

The height which an individual achieves is determined largely by the rate of growth. A child destined to become a tall adult grows at a rate consistently rather greater than his third centile peer. It is now well recognised that growth rate is determined by the amplitude of pulsatile growth hormone secretion.[2] What this means is that just as height velocity is a continuous variable, so also is growth hormone secretion. Thus the idea that there is a cut off value for either of these

Table 1 Tests of growth hormone secretion

Screening tests:	
Serum insulin like growth factor-1 concentration	
Exercise	
Physiological tests:	
24 hour profile	
Sleep study	
Urinary growth hormone excretion	
Pharmacological tests:	
Insulin induced hypoglycaemia	L-dopa
Arginine	Clonidine
Glucose	Glucagon
Growth hormone releasing hormone	

One of the major problems is that the growth hormone axis is very sensitive and the reproducibility of results in individual children is only ±35%, as opposed to group data which are much more reliable. Further, children growing slowly as a result of gastrointestinal disease, respiratory disease, or renal disease often have depressed concentrations of growth hormone to any stimulus. Our view, therefore, is that the physician seeing a child growing slowly should decide whether or not an endocrine cause is likely and if there is a serious worry about an insufficiency of growth

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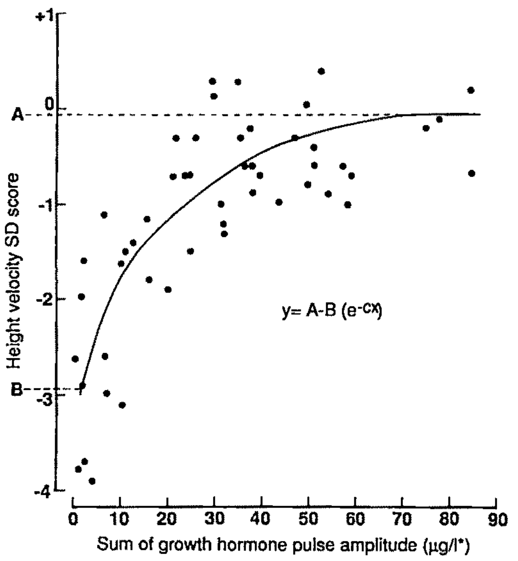

*Figure 1 Association between growth hormone secretion and height velocity in 50 short prepubertal children.[9] *Growth hormone conversion factor 1 µg/l=2 mU/l.*

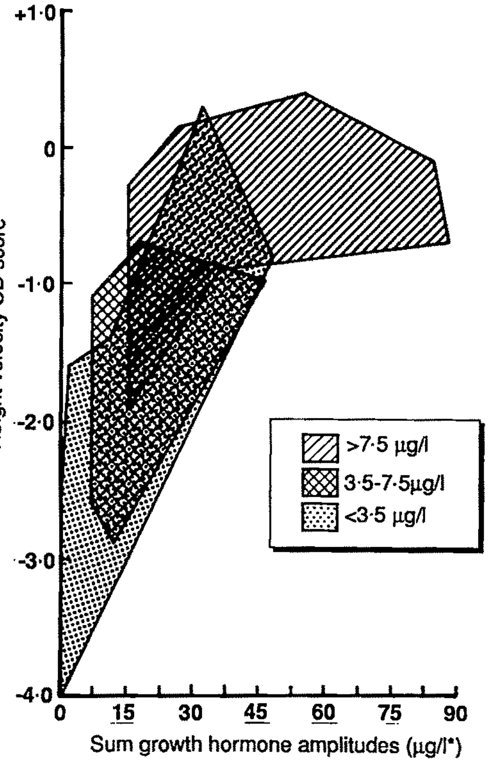

*Figure 2 Results of tests of peak response of growth hormone to insulin induced hypoglycaemia in the same 50 children. *Growth hormone conversion factor 1µg/l=2 mU/l.*

Interpreting the results

We have already made clear that growth velocity is the most sensitive indicator of an abnormality of growth hormone secretion. In order to grow along the third or 97th centile on a height distance centile chart, a patient needs to have a growth velocity between −0·8 and +0·8 standard deviations year on year, which is the mathematical basis for the Middlesex height velocity chart. When one compares the results of growth hormone tests against such a gold standard criterion, one can come up with estimates of sensitivity and specificity that vary according to the cut off point which is chosen to represent normality (table 2).

Table 2 The effect of employing cut off values to test results in 64 children

	Height velocity SD score		*Sensitivity in detecting true positive*	*Specificity in excluding true negative*
	<−0·8	*>−0·8*		
Peak growth hormone responses to insulin induced hypoglycaemia (µg/l*):				
<7·5	35	5	87·5%	83·3%
> 4	4	20		
<5·0	27	1	96·4%	66·6%
>5·0	12	24		

*Growth hormone conversion factor 1µg/l=2mU/l.

Further difficulties are imposed by the demonstration that the state of the hypothalamo-pituitary axis before the peformance of a test has an important influence on its result. Every test is designed to test the readily releasable pool of growth hormone that happens to be in the pituitary at the time the test is performed. If there has recently been a pulse of growth hormone secretion and the gland is empty, nothing will make it produce a further response. A high baseline value in a provocative test may presage a misleading result. In a patient in whom there is an abnormality of the control of growth hormone secretion (neurosecretory dysfunction), a pharmacological test may falsely suggest that growth hormone secretion is normal when in fact the pattern is grossly disorganised. Nutritional state is also important: in states of starvation (intrauterine growth retardation) growth hormone concentrations are high and responses to stimuli are blunted in obese children growing quite normally.

The second common situation in which tests may be misleading is in late prepuberty. The pubertal increase in growth hormone secretion requires an increase in sex steroid concentration and tests of growth hormone secretion done in patients over 11 years of age need very special consideration.

Finally, as indicated, many conditions that interfere with growth have secondary effects on growth hormone secretion. The correction of the basic abnormality (gluten free diet or removal of a child from an inclement emotional environment) will restore growth hormone secretion.

Who needs tests of growth hormone secretion?

All this brings us back to what the point of such tests were in the first place. It is now abundantly clear both from the implication in figs 1 and 2 and from clinical practice[7] that any child given growth hormone will grow more quickly. The amount of growth hormone that has to be given is determined by the pretreatment rate at which the children are growing (the most slowly growing, the most severely insufficient of growth hormone secretion will respond best), the dose of growth hormone used, and the condition being treated.[8] The only reason for a test of growth hormone secretion is therefore to confirm that the problem lies in this area and not elsewhere; we have already seen that the tests do not achieve this result.

A plan for action

It will be clear that tests of growth hormone secretion are currently in a mess and we purpose the following scheme for the management of the short child seen in general paediatric practice:

(1) Measure the child and the heights of his parents. In the absence of other indications:
(2) Measure the child again after four months and calculate an annual growth velocity.
(3) Plot the velocity on the Middlesex height velocity chart.

(4) If the velocity is way below the lower limit of normal (third centile), take immediate action.
(5) If the velocity is close to the lower limit of normality (third to 25th centile), follow up the child for a longer period of time.
(6) In cases of doubt, the paediatrician has the option of either giving the child growth hormone or seeking advice from a specialist centre.

In these days of cost consciousness, the latter is likely to be a cheaper option for the referring health district than the former.

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Archives of Disease in Childhood 1991; **66:** 88–90

Ethnic differences in infant health

Ethnic minorities are people and communities with distinct national origins, ways of life, languages and/or religions that differ from those of the majority. Although skin colour is not explicit in this definition, the communities on whom attention has focused in terms of their health do not have white skin. On account of their skin colour and culture, black people and ethnic minorities are discriminated against in many areas of social and economic life, directly and indirectly, resulting in restricted opportunities and generally lower socioeconomic status.[1]

In the UK, consistent patterns have emerged in local and national reports of 'ethnic' differences in infant health. Reports of such differentials must, however, be compared and interpreted carefully. Terminology and categories have not always been used consistently, and data have been analysed and interpreted with varying degrees of rigour, insight, and sophistication.

Categories and terminology

Clarity, specificity, and accuracy are imperative in clinical practice and epidemiology. In the complex area of ethnicity and race relations, it is particularly important to clarify terms. The accuracy and empirical basis of categories used are not always clear. Whereas some studies clearly use country of birth to define group membership,[2 3] others report data for ethnic groups without stating clearly how they were defined.[4–6] In contrast to the Registrar General's *Classification of Occupations*, on the basis of which people can be assigned to a social class, there are no universally agreed definitions or categories of ethnic groups. There have been understandable objections to the very notion of official ethnic or racial categories, but recently there has been increasing recognition that discrimination and disadvantage cannot be monitored without appropriate data. Despite the limitations of reducing the complexities within communities to simplistic categories, most government social surveys now include an ethnic question, as will the population census for the first time in 1991. Taken together with other socioeconomic indicators, such ethnic categories can highlight inequalities in health which social class alone cannot convey.

THE LIMITATIONS OF AGGREGATE TERMS

Aggregate terms that refer to skin colour or continental origins are of questionable validity because they mask national, social, and economic differences within the group. For example, a bland 'Asian' category would include people from Pakistan, Bangladesh, India, and its diverse regions, and people from East Africa whose ancestors originated in the Indian subcontinent. In one study, the 'Asian' category included infants of Chinese origin.[4] However, in England and Wales there is greater variation in infant health within the 'Asian' group than between mothers born in the UK and the constituent Asian national categories.[2 3 7]

NATIONAL ORIGIN

In their turn, categories such as 'British' or 'Indian' which may refer to country of birth or to ancestral origins also subsume social and economic complexity. Several studies have taken their analysis further, looking at religion,[8] and establishing the effect of confounding biological and social variables.[2 3 7 9 10] Local data sets based on a single health district or maternity hospital may not be large enough to permit such complex analysis unless several years' data are grouped together.[6 11] Such local studies can, however, identify variations from national trends.[6 9 10]

COUNTRY OF BIRTH AS A SURROGATE

In the UK, country of birth is decreasing further in its limited adequacy as a surrogate for ethnic group, as an increasing proportion of minorities are born here. While the number of British born ethnic minority mothers may be statistically negligible at a national scale,[2 3] in several cities such as Liverpool, Cardiff, and London, black and other minority communities have been established for several generations. The exclusion of information on ethnicity from routine data systems in the health service is thus regrettable.

Perinatal mortality

Comparison of perinatal mortality in England and Wales for 1975–85 by mother's country of birth showed persistently high rates among births to mothers born in Pakistan.[2] Moreover, their high mortality continues throughout infancy.[3] Adjustments for biological and social factors reduce, but do not eliminate, their excess mortality and congenital abnormality rates. The difference in perinatal mortality between births to women born in the UK and those to all other immigrant mothers narrowed during the decade. For 1982–5, perinatal mortality among births to mothers born in Pakistan was almost twice the rate for UK born and Irish mothers, and was considerably higher than for births to other immigrant women from the New Commonwealth. Excess perinatal mortality among births to mothers from the New Commonwealth and Pakistan generally persisted across age groups, parity, and social classes.

Only one study, which employed aggregate 'Asian' and 'non-Asian' categories, has estimated the combined effect of several confounding variables, including obstetric experience of the woman's general practitioner.[10] After adjustment for social class, parity, height, legitimacy, and general practitioner obsteric list status, the relative risk of perinatal death among 'Asian' women was reduced from 165 to 142.

CAUSE OF PERINATAL DEATHS

Congenital malformations accounted for almost a third of Pakistani perinatal deaths in England and Wales in 1982–5, compared with less than a quarter for Bangladeshi, Indian, East African, Irish, and UK born mothers' births.[2] By contrast, perinatal deaths from congenital anomalies were least common in births to mothers from West Africa and the Caribbean. This deficit of congenital malformations among Afro-Caribbean babies was not so noticeable in a study from

London,[9] but was identified in Birmingham,[6] which also reflected the national trend of high perinatal mortality from congenital anomalies in Pakistani births, with an increased rate of multiple and chromosomal abnormalities. In Leicestershire, the relative risk of perinatal death from congenital malformations was 158 for 'Asian' women, compared with 'non-Asian' case controls.[10] In Bradford, where the Asian population is predominantly of Pakistani origin, stillbirth and early neonatal death rates from congenital abnormalities were twice and almost four times higher respectively in 'Asians' than in 'non-Asians', with multiple congenital abnormalities particularly prominent.[5]

Several studies analyse perinatal mortality rates and congenital malformation rates by separate confounding biological and social factors.[2 5 7 9] In most instances, each of the confounding factors reduces, but rarely eliminates, excess mortality. In Bradford, disaggregation of combined stillbirth and infant mortality rates by social class eliminated the difference between 'Asian' and 'non-Asian' deaths *not* associated with congenital abnormality.[5] In social classes IV and V, which included 70% of 'Asian' mothers, a twofold 'Asian' excess remained in deaths from congenital abnormality.

Postneonatal mortality

Although over 40% of all infant deaths occur in the postneonatal period,[3] ethnic differences in postneonatal mortality have received scant attention. In contrast to the

[redacted]

Hindu babies were still lighter. Further analysis comparing mother's country of birth identified lighter babies among Hindus from East Africa than those from India. By contrast, a study from Birmingham identified a significantly high incidence of very low birth weight (<1500 g) in 'West Indian' births, compared with births to 'European' and 'Pakistani' mothers.[11] The number of births in the study was too small to permit inclusion of Bangladeshi births or analysis of confounding variables.

PHYSIOLOGICAL OR PATHOLOGICAL?

There has been some debate as to whether the higher incidence of low birth weight in some minority communities is pathological, or whether it is indicative of physiological differences between groups.[8 11] In England and Wales for 1982–5, perinatal mortality for low birthweight babies was lowest in babies of women from East Africa (66), India (68), Bangladesh (81), and the Caribbean (84), but was highest (115) among low weight births to Pakistani mothers.[2] In the Birmingham study, lower neonatal mortality among very low birthweight 'West Indian' babies corroborated suggestions from America that birth weights are physiologically lower among black than white babies.[11 12] However, a study from south east London which compared 'British', 'West Indian', and 'African' births found no significant difference in perinatal mortality among very low and low birthweight babies.[9] Other studies in west London have identified significantly low perinatal mortality among low birthweight

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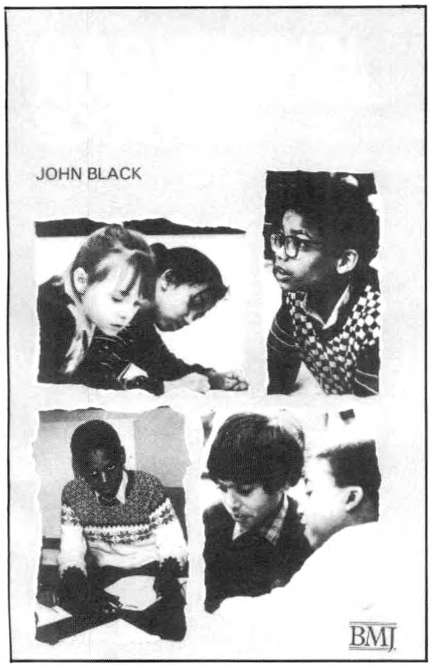

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Archives of Disease in Childhood 1991; **66:** 91–92

Neuroleptic malignant syndrome

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ORIGINAL ARTICLES

Elemental diet for refractory atopic eczema

J Devlin, T J David, R H J Stanton

Abstract

A total of 37 children with refractory widespread atopic eczema were treated with an antigen avoidance regimen comprising hospitalisation, exclusive feeding with an elemental formula for a median duration of 30 days, and measures to reduce exposure to pet and dust mite antigens at home. After the initial period of food exclusion, food challenges were performed at intervals of seven days, and the patients followed up for at least 12 months. Ten of the children (27%) either failed to respond to the regimen or relapsed within 12 months. Improvement in the eczema was seen in 27/37 (73%) patients, by discharge from hospital their disease severity score had fallen to a median of 27% of the pretreatment figure, and only 3/27 required topical corticosteroids. There were no clinical or laboratory findings which could be used to predict the outcome. Drawbacks to the regimen were prolonged hospitalisation (median 70 days), a fall in body weight and serum albumin concentration, and a risk of anaphylactic shock (4/37 cases). A strict antigen avoidance regimen may be associated with improvement of atopic eczema where conventional treatments have failed.

A small proportion of children with atopic eczema remain severely handicapped with severe and widespread eczematous skin lesions. This may happen despite the most intensive application of conventional treatment,[1] such as emollients, topical steroids, antibiotics for infection, bedtime sedating antihistamines, and avoidance of allergic (for example, pets or foods[2]) or non-allergic (for example, heat or woollen clothing) triggers that have been identified from the history. In such extreme cases, the traditional additional therapeutic options are unappealing. They comprise the application of potent topical steroids to large areas of skin, with the risk of skin atrophy and growth stunting, the use of systemic steroids, with the risk of growth stunting, cataract, osteonecrosis and other side effects, or doing nothing and leaving the child chronically handicapped and unable fully to engage in normal activities. Recent experimental approaches are no more attractive. Photochemotherapy has been tried in a small number of cases with some success, but problems include severe irritation during treatment requiring systemic steroids, relapse after treatment, and the increased long term risks of skin cancer and cataract formation.[3 4] Oral cyclosporin has been used with dramatic benefit in a few adult cases of atopic eczema,[5] but return of disease after stopping treatment, and risks of renal toxicity and lymphoma production are major drawbacks. Topical cyclosporin appears less effective.[6] Anecdotal reports of treatment with cytotoxic agents (cyclophosphamide, azathioprine, mustine, thioguanine, and aminopterin) describe temporary benefit, but bone marrow toxicity, lymphoma production, and sterility are deterrents to the use of these agents. Interferon gamma has been tried, with some degree of benefit,[7] but the temporary nature of the improvement and the need for injections are drawbacks.

Where a case of atopic eczema is refractory to conventional treatment, the question arises as to whether part or all of the disease can be attributed to allergic reactions to items such as food, pets, or dust mites. Accordingly, and only as a last resort, we have in exceptionally difficult cases tried an extreme antigen avoidance regimen, which comprises a prolonged so called elemental diet while in hospital, accompanied by measures to reduce exposure to pet and dust mite antigens upon return home. We report on 37 children with severe atopic eczema who were treated in this way.

Patients and methods

Since 1980, 600 children with atopic eczema, who fulfilled the diagnostic criteria of Hanifin and Rajka,[8] have been referred to the Department of Child Health at Booth Hall Children's Hospital. In 43 of these the disease was widespread and severely handicapping, the condition had failed to respond to conventional topical treatment[1] and dietary regimens,[2] and the patient was considered for an extreme antigen avoidance regimen including an elemental diet in hospital using Vivonex (Tolerex) Standard (available from Norwich Eaton Pharmaceuticals, 17 Eaton Avenue, PO Box 231, Norwich, NY 13815, USA). One family declined this approach, and two children aged 4 and 11 years refused to drink Vivonex so the procedure was abandoned. We present data on the 37/40 patients who have been followed up for 12 months or longer.

ANTIGEN AVOIDANCE MEASURES AT HOME

Removal of all mammalian and avian pets from the home was a prerequisite for treatment and was undertaken in 13 patients. The home was visited by TJD or JD to ensure that rigorous measures (described elsewhere[1]) were taken to reduce house dust mite levels in the patient's bedroom.

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PATIENT MONITORING

The percentage of skin surface area affected by eczema and the degree of erythema (graded as mild=1, moderate=2, severe=3) were multiplied to give a combined disease severity score. Assessments were made by TJD or JD on admission to hospital, at the end of the period of exclusive feeding with Vivonex, at the time of discharge from hospital, and at follow up visits. Topical corticosteroids were classified according to the *British National Formulary*[9] as category IV (mildly potent), category III (moderately potent), category II (potent), or category I (very potent).

Laboratory tests for specific IgE antibodies, radioallergosorbent (RAST) tests, were performed on admission, using a panel of 15 to 30 (depending on availability) common foods and other antigens. During hospitalisation, twice a week measurement was made of the serum proteins, electrolytes, and absolute eosinophil counts, and weekly measurements were made of the serum IgE concentration.

OTHER TREATMENT

Corticosteroids were discontinued at the time of admission. Simple emollients (usually emulsifying ointment) were applied topically when necessary. Trimeprazine tartrate, an H1 receptor antagonist, which had been used in a dose of 3 mg/kg (to a maximum of 60 mg) by all patients before admission for night sedation, was continued. Because of the poor palatability of unflavoured Vivonex, cyproheptadine, an H1 receptor antagonist with some appetite stimulant effect,[10] was also given until food was reintroduced, in a dose of 2 mg twice a day.

DIETARY MANAGEMENT

All normal food and drink (including water) were excluded, and the child was fed exclusively on unlimited quantities of unflavoured Vivonex. To minimise the possibility of osmotic diarrhoea, patients were started at a low concentration (6·7 g/100 ml, 140 mOsm/kg), gradually increasing to isotonicity (13 g/100 ml, 280 mOsm/kg) on the third day. If this did not provoke loose stools, the concentration was increased further to a maximum of 26·7 g/100 ml (560 mOsm/kg). The first three patients received Vivonex alone for 7, 16, and 17 days respectively, but this was lengthened to a minimum of four weeks in all subsequent patients. This was partly because it was found that in most patients noticeable improvment only occurred after four to six weeks, and also because an incomplete response made the subsequent interpretation of food challenges much more difficult.

After 28 days of Vivonex given alone, if there was little or no improvement the diet was abandoned, and systemic or topical corticosteroids were used instead. If there was a moderate improvement the period of elemental diet was extended for another one to two weeks. If the eczema had largely resolved, then open food challenges were commenced. Foods to which the patient had a history of adverse reaction, and cows' milk, eggs, wheat, fish, nuts, tomato, citrus fruits, and legumes were deliberately avoided for early challenges. In hospital, each new food was given in quantities of 50 to 200 g two to four times a day for a period of seven days.

During this time the patient's skin was observed every four hours for deterioration, and other indications of intolerance such as respiratory or gastrointestinal symptoms were noted. The criteria for a positive challenge were (1) a sustained deterioration of eczema (increased scratching and visible worsening of eczematous skin lesions, lasting more than 24 hours), or other adverse reaction (for example, angioedema or asthma) during exposure to the food, and (2) a return to the prechallenge state after the food was withdrawn. If the second criterion was not met, the challenge was not classified as positive or negative, the food was avoided, and a repeat challenge was performed at a later date.

DISCHARGE FROM HOSPITAL AND OUTPATIENT FOLLOW UP

Patients were discharged from hospital once established on three foods, at which point Vivonex was discontinued. For the first week at home no food challenges were performed, and the child was kept indoors to ensure that the home environment did not provoke eczema. Food challenges were then continued at home and when positive the challenge was repeated at intervals of six to 12 months. All diets were supervised by a paediatric dietitian (RHJS). After discharge from hospital, the nutritional adequacy of the diet[11 12] was monitored by means of five day diet surveys.[13] If by three months after discharge the dietary intake of calcium was below the recommended daily amount,[14] oral calcium supplements were given in the form of tablets containing calcium sodium lactate and calcium phosphate.

Results

Details of the patient's age, pretreatment severity of eczema, duration of the hospital admission, duration of use of Vivonex, maintenance concentration of Vivonex, and lowest serum albumin are given in table 1. The patients were followed up for between one and eight years, and table 2 gives details of eczema and asthma severity, treatment, and diet during six years of follow up. Thirty five out of 37 (95%) patients had a raised (compared with age related normal values) pretreatment serum IgE concentration, median 12 500 kU/l (range 11 to 224 000 kU/l). During the Vivonex only period there was no correlation between change in disease severity and change in serum IgE concentration. Spearman's rank correlation coefficient r=0·02. Taking $0·44\times10^9$/l as the upper limit of normal for the absolute eosinophil count, 33/37 patients had a pretreatment eosinophilia.

TREATMENT FAILURE

(a) Non-responders

In four patients (three were girls), the disease

Table 1 Age of patients, pretreatment disease severity, duration of hospitalisation, strength of Vivonex, and lowest serum albumin concentration

	Age (years)	*Pretreatment state of eczema*			*Days in hospital*	*Days on Vivonex alone*	*Total days on Vivonex*	*Maintenance concentration of Vivonex (g/l)*	*Lowest serum albumin (g/l)*
		Surface area (%)	*Erythema score* (%)*	*Combined score†*					
Median	3·32	70	3	210	72	30	62	16·7	20
Range	0·45–13·23	20–96	2–3	60–288	45–189	7–43	7–124	13·3–26·7	9–32‡

*1=Mild, 2=moderate, 3=severe.
†Combined score=surface area×erythema score.
‡Not recorded in 10 patients.

Table 2 Progress of disease severity, treatment, diet, and asthma severity during hospitalisation and follow up

Time	*Start Vivonex (n=37)*	*End Vivonex (n=37)*	*Discharge home (n=37)*	*Hospitalisation/follow up*							
				6 weeks (n=37)	*6 months (n=37)*	*1 year (n=37)*	*2 years (n=31)*	*3 years (n=25)*	*4 years (n=16)*	*5 years (n=12)*	*6 years (n=9)*
Disease severity score ratio:*											
Median		0·33†	0·22	0·24	0·17	0·07	0·05	0·01	0·02	0	0
Range		0·03–1·34	0–0·75	0·01–1·27	0–1·00	0–1·18	0–0·63	0–0·31	0–0·36	0–0·32	0–0·23
No (%) on topical corticosteroid treatment:											
None	0	36 (97)	27 (73)	27 (73)	22 (59)	20 (54)	17 (55)	16 (64)	11 (69)	9 (75)	8 (89)
Category IV	17 (46)	0	4 (11)	4 (11)	4 (11)	6 (16)	8 (26)	7 (28)	4 (25)	3 (25)	1 (11)
Category III+	16 (43)	1 (3)	3 (8)	3 (8)	7 (19)	7 (19)	3 (10)	1 (4)	1 (6)	0	0
Systemic	4 (11)	0	3 (8)	3 (8)	4 (11)	4 (11)	3 (10)	1 (4)	0	0	0
Diet score:‡											
Median		7	7	7	6	6	5	4	3	2·5	3
Range		7	3–7	5–7	1–7	1–7	1–7	1–5	1–5	1–5	1–5
No (%) on asthma treatment:											
On any treatment	19 (51)	19 (51)	20 (54)	21 (57)	23 (62)	25 (68)	22 (71)	19 (76)	10 (62)	9 (75)	7 (70)
On inhaled steroids	2 (5)	3 (8)	3 (8)	3 (8)	3 (8)	4 (11)	7 (23)	10 (40)	8 (50)	7 (58)	7 (70)

*Disease severity score expressed as a fraction of starting disease severity score (surface area×severity)
†Diet score: 1=normal, no exclusions; 2=excludes one or two foods; 3=excludes three to five foods; 4=excludes six to 10 foods; 5=excludes more than 10 foods, includes more than 20 foods.
‡Significant improvement, p<0·001 (Wilcoxon matched pair signed rank test on actual values).

severity score at the end of the Vivonex only period was the same as, or higher than, the starting score, and three patients were started on systemic corticosteroids.

(*b*) *Late failures*

Late failure was defined as improvement on Vivonex, followed by relapse within 12 months requiring either systemic corticosteroids or category III or II topical corticosteroids to areas other than the hands or feet. Six patients (all boys) showed an early improvement but later deteriorated. Two of these patients, who had previously been receiving systemic corticosteroids, had to recommence treatment with oral prednisolone at six months and three years respectively. The other four patients relapsed to their pretreatment state between six weeks and six months after discharge, and required widespread application of category III or II topical corticosteroids.

These 10 treatment failures were compared with the 27 in whom there was a sustained improvement (table 3). No significant difference was found for age, sex, pretreatment disease severity score, previous history of food intolerance, pretreatment eosinophil count, or serum concentration of IgE. The median fall in serum albumin concentration in the four early non-responders was 17·5 g/l. This was significantly greater than the median fall (7 g/l) in the 17 patients who responded and in whom it was measured (p<0·01, Wilcoxon rank sum test).

Table 3 Characteristics of patients who improved on Vivonex compared with those who did not improve

	Improved (n=27)	*Not improved (n=10)*	*p Value*
Age:			
Median	3·2	3·5	>0·1*
Range	0·4–13·2	2·3–8·7	
Sex:			
No (%) of males	14 (52)	7 (70)	0·27†
Pretreatment disease severity score:			
Median	210	202	>0·1*
Range	75–288	60–285	
No (%) with previous history of food intolerance:			
	16 (59)	6 (60)	0·63†
Pretreatment serum IgE concentration (kU/l):			
Median	12 600	7400	>0·1*
Range	87–224 000	11–164 000	
No (%) in whom serum IgE concentration fell during Vivonex only period:‡			
	11/15 (73)	4/9 (44)	0·16†
Pretreatment eosinophil count (×10⁹/l):			
Median	0·994	1·016	>0·1*
Range	0·063–5·302	0·550–2·592	
No (%) in whom eosinophil count fell during Vivonex only period:§			
	11/26 (46)	7/10 (70)	0·13†

*Wilcoxon rank sum test; †Fisher's exact test.
‡Not recorded in 13 patients.
§Not recorded in one patient.

The median fall in serum albumin concentration in the six late failure patients (13.5 g/l) was also greater than in the patients who responded to treatment, but the difference was not significant (p>0·1).

TREATMENT SUCCESS

In 27/37 (73%) patients there was sustained improvement in the eczema. With one exception, where clear improvement was seen within seven days of commencing the elemental diet, the first signs of improvement were not seen for at least one, and more commonly two weeks. It was usually only after four weeks of exclusive feeding on Vivonex, however, that there was substantial improvement in the appearance of the skin lesions. The greatest improvement occurred during the period on Vivonex alone, when the median disease severity score fell to 27% of the pretreatment score (range 3 to 67%). Before treatment, 14/27 (52%) had been using category IV topical corticosteroids, 12/27 (44%) had been using category III or II topical corticosteroids, and one patient was receiving oral prednisolone. At the end of the Vivonex alone period, 26/27 (96%) were using emollients only, and the remaining patient was using a category III topical corticosteroid for small areas of eczema.

This improvement continued in 17/27 (63%) patients while foods were reintroduced in hospital, and this reduced the median severity score to 18% of the pretreatment score by the time of discharge from hospital. This further improvement was significant (Wilcoxon matched pair signed rank test on actual values, $p=0{\cdot}01$). By discharge from hospital, 24/27 (89%) patients remained on emollients alone, and two patients commenced category IV topical corticosteroids. Follow up details are given in table 2.

ADVERSE EVENTS DURING ADMISSION TO HOSPITAL

Details for weight were not recorded in three early patients. Of the remaining 34, 30 (89%) lost up to 17% of their body weight while taking Vivonex alone (<5%, 4; 5–10%, 16; >10%, 10). Seven children developed loose stools while on Vivonex, but no patient developed abnormal concentrations of serum electrolytes. After hypoalbuminaemia was noted in one child, the serum albumin was routinely measured. The serum albumin fell in 25/27 patients from a mean (SD) of 30·8 (6·0) g/l on admission to a mean nadir of 21·2 (7·2) g/l. The lowest serum albumin was not significantly related either to the duration of the elemental diet (Spearman's rank correlation coefficient, $r=-0{\cdot}076$, $p=0{\cdot}71$) or to the concentration of Vivonex used ($r=0{\cdot}024$, $p=0{\cdot}89$), but was significantly correlated with the combined disease severity score at the start of treatment ($r=-0{\cdot}48$, $p=0{\cdot}013$). Six children obtained forbidden food on one or two occasions, and one child was covertly given normal food by a grandparent for two weeks before this was discovered. None of these seven children were in the 'early failure' group (see below).

FOOD CHALLENGES IN HOSPITAL

A total of 185 challenges were performed in the 37 patients. Twenty had no reactions to a total of 79 challenges, but the other 17 had a total of 40 (median per child 2, range 1 to 7) reactions to 13 foods out of a total of 107 challenges.

(a) Reactions occurring within one hour

Five children exhibited reactions within an hour of eating a food. One developed anaphylactic shock (with urticaria and bronchoconstriction) within 15 minutes of eating peas (RAST score to peas grade 3),[15] and another developed anaphylactic shock within 20 minutes of taking a feed of comminuted chicken (RAST score 3).[16] Another child had an itchy erythematous rash, wheezing, and rhinitis within 30 minutes of eating potato (RAST score 0). A fourth child had an erythematous rash within an hour of eating corn (RAST score 2). A fifth child developed generalised pruritus and periorbital oedema within minutes of eating lamb (RAST test not performed).

(b) Delayed reactions

The other 35 reactions consisted of a deterioration in the patient's eczema, with a noticeable increase in itching and erythema, and a return to the prechallenge state after the food had been withdrawn. Seven of these reactions occurred between one and 24 hours of starting the food, four began between 24 and 48 hours after starting a food, and 24 (61% of all food reactions in hospital) were first noted only two to seven days after introduction of the food. These reactions were to lamb (n=6), corn (n=6), rice (n=4), potato (n=3), Pregestimil (a casein hydrolysate infant milk formula, Bristol-Myers) (n=3), avocado (n=3), carrot (n=2), banana (n=2), chicken (n=2), pea (n=1), pork (n=1), rabbit (n=1), and bean (n=1). The RAST score was known for 17 of these foods and was 0 in 11 positive challenges, 1 in one, 2 in two, and 3 in three.

FOOD CHALLENGES IN THE FIRST 12 MONTHS

The results of 853 food challenges were recorded from the end of the elemental diet to one year after discharge in the 37 patients. The median number of challenges per patient was 24. Two hundred and five (24%) of the recorded challenges were positive (median number per patient 5, range 0 (in one patient) to 19).

REACTION TO PETS, HOUSE DUST MITES, AND GRASS

Formal challenges were not performed, but after discharge from hospital a clear history of an allergic reaction was noted in 19/37 (51%) patients: cat (n=8), dog (n=17), house dust (n=6), hamster (n=3), horse (n=3), pet bird or feathers (n=3), guinea pig (n=2), rabbit (n=2), cow (n=1), and skin contact with grass (n=13).

Discussion

The aim of this regimen was to achieve a period in hospital of near complete antigen avoidance, and to maximise the avoidance of relevant antigens during follow up. The chief obstacles were the unpleasant taste of the elemental formula and difficulty in avoidance of inhalant antigens. In fact most children drank the formula after a short period (less than 24 hours) of refusal, and were helped by understanding the aim of the diet. Some children preferred the formula warm, others cold, and two would only take it in the form of ice lollies or crushed ice. Nevertheless, constant scrutiny and encouragement by the nurses and dietitians was required to ensure an adequate intake, and also to prevent other residents on the ward from leaving food or drink accessible to the patient. In one case taps had to be removed in the patient's cubicle to prevent the child drinking water instead of formula, and two children completely refused to drink the formula and in these the regimen was abandoned. Measures to reduce exposure to house dust mites[1] and pets at home were an integral part of the regimen. The former often entailed considerable expense (for example, replacement of bedroom carpet by cushion flooring; replacement of bed base by non-divan type of bed). The need to remove pets was usually most unpopular, and was sometimes seen by parents to be a greater problem than a period of two to three months of hospitalisation. Most families were helped by a pretreatment visit to another family who had been treated with the regimen, and who were often able to describe exacerbations of eczema after pet exposure and which had only been noted once the eczema had improved while on the regimen. Avoidance of inhalant antigens such as pollens or mould spores was not attempted.

Elemental diets are potentially hazardous. Weight loss despite a theoretically adequate (that is, above the recommended daily amount[14]) intake in 30/34 (89%) and a reduction in the serum albumin in 25/27 (93%) were the most commonly encountered problems. These probably reflect the increased metabolic demands of a child with widespread and long standing skin inflammation. Loose stools occurred in 7/37 (19%), were attributed to the hypertonicity of Vivonex, and responded to a reduction in concentration. The occurrence of four cases of anaphylactic shock emphasises the potential hazards of food challenges in children with food allergy. This aspect is discussed elsewhere.[15–17] Thirty patients received hypertonic concentrations of Vivonex. It has been shown in rats that hypertonic feeds may cause increased jejunal permeability to macromolecules[18] and structural damage to jejunal microvilli.[19] It is theoretically possible that the former could contribute to a severe hypersensitivity reaction during a food challenge. Such speculation does not have to be invoked to explain our cases of anaphylactic shock, however, which is a well recognised hazard for some children with food allergy.[16]

As far as assessing the benefit of this antigen avoidance regimen, there are three main drawbacks to our methodology. The lack of a control group means that it is not possible to assess how much improvement was due to a placebo effect. It would be desirable, but impractical, to have a control group of patients admitted to hospital for several months but given instead a liquid preparation of normal food, and it would be impossible to disguise the poor flavour of Vivonex. An alternative would be to conduct a randomised study, with half the patients being randomised to a non-treatment arm, and this would be informative for there are no data on the natural history of exceptionally severe atopic eczema. This is important, for in a recent study of a less demanding dietary regimen in a group of less severely affected children with atopic eczema, the outcome at 12 months was the same regardless of response to diet.[20] It is a common but undocumented observation that atopic eczema sometimes improves swiftly after admission to hospital, whether or not topical corticosteroids have been continued. The usual suggested explanations for this are noncompliance with topical treatment at home, or removal from potential sources of antigens in the home such as pet animals or house dust mites.[21] The observation that in the present study recovery was rather slow, and continued after discharge, suggests that none of these explanations account for the improvement that occurred in hospital in our patients.

The second methodological drawback is that our patients do not represent a homogeneous category, and were selected solely on the grounds of severity and lack of response to conventional treatment. It is clear that only some of this group are potential responders to antigen avoidance regimens, and it is most unsatisfactory that we were unable to identify any biochemical, immunological, or historical marker that would predict the outcome of the regimen. The difficulty in identifying those who are likely to respond to dietary elimination has been noted before.[22]

The third problem that bedevils all studies of atopic eczema is the lack of an objective method for assessing disease severity. We attempted to use limb movement meters,[23] but found that their use was associated with a considerable increase in skin damage, children using them as an additional implement while scratching. For scoring disease severity, we combined an estimate of the surface area of affected skin with a subjective assessment of the severity of inflammation. We previously found that this combined score was correlated more closely with biochemical markers of disease severity such as the serum orosomucoid concentration than measures of the surface area alone.[24] Although this type of scoring system is partly subjective, and does not exclude observer bias, it does eliminate the problem of fluctuation of symptoms such as itching and scratching.

It is generally agreed that double blind, placebo controlled food challenge with tiny quantities of encapsulated freeze dried foods is the best method for confirming adverse reactions to foods.[17] Nevertheless, there are a number of circumstances where such challenges may give a misleading and incorrect result.[15] Our challenges were not performed blind, but double blind challenges with normal food portions would be difficult to perform in a child receiving Vivonex alone, where a new food could not be disguised in a 'carrier' food. The alternative

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option of feeding via a nasogastric tube would be unacceptable to most children, and would bypass the oral mucosa, possibly leading to a false negative reaction.[25] Finally, double blind challenges for three foods, using a seven day period for active challenge, placebo and washout, and repeated three times to reduce the probability of error,[26] would have extended the period of hospital admission by more than two months. Although we used open challenges, the circumstances were such as to favour a negative challenge, and avoid false positive results. Foods *least* likely to produce an adverse reaction were deliberately chosen for challenges, so that children could be discharged from hospital and then established on a reasonable diet as quickly as possible. The patients were strongly motivated to tolerate new foods, having been in hospital for a month or more on a highly unpalatable liquid diet. Such circumstances do not exclude bias and overdiagnosis of food allergy, but the lack of double blind methodology cannot explain away the 40 adverse reactions witnessed by nursing and medical staff in hospital and followed by improvement after food withdrawal. The data on outpatient challenges are less secure because they were not supported by constant nursing and medical observation.

Twenty eight of the 40 reactions occurring in hospital in this study did not commence until at least 24 hours after the patient had started to take the food. Delayed reactions resulting in atopic eczema have been repeatedly reported.[27–30] It is possible that some of these delayed reactions are late phase IgE mediated reactions,[12 31–34] attributable to an IgE triggered cascade of infiltration by eosinophils and neutrophils, deposition of eosinophilic major basic protein, release of proinflammatory mediators, and infiltration by monocytes and lymphocytes.[35 36] However, the lack of correlation between challenges and RAST tests in the present study suggests that most delayed reactions were mediated by mechanisms which do not involve specific IgE antibodies. Finally, it is possible that the long term use of trimeprazine, an H1 antagonist, may have masked some immediate reactions.

Despite several limitations, the present study has demonstrated that a highly intrusive (minimum hospitalisation two months) and potentially hazardous antigen avoidance regimen was associated with great benefit in some children previously handicapped by refractory, widespread atopic eczema. In the present series, 27 of 37 (37%) such children experienced sustained improvement, although in none did the eczema disappear completely. In four (11%) patients the treatment failed outright, and in six (16%) an initial improvement was soon followed by relapse and return to the pretreatment state. It is not possible to estimate how much benefit was due to food or other antigen avoidance. Adverse reactions to pets, house dust, and grass were noted in 19/37 (51%) patients after discharge from hospital. The slow rate of improvement seen in this study, however, contrasts with the undocumented but often observed rapid improvement seen when some patients go on holiday or are admitted to hospital. This suggests that avoidance of environmental antigens was not the major factor causing improvement in our patients.

Recent paediatric[2] and dermatological[37] estimates are that no more than 10% of children with atopic eczema severe enough to warrant referral to hospital are likely to derive lasting benefit from the use of an elimination diet. In the sole previous study of the use of an elemental diet in the treatment of atopic eczema in childhood, seven children received an elemental feed for only two weeks.[38] This was followed by six other foods for four weeks. The eczema score improved considerably in six, but in four of these there was little deterioration after returning to a normal diet. In a recent study of 25 children with atopic eczema, either a whey hydrolysate milk formula or Vivonex was given for one to two weeks followed by challenges with foods and food additives. It was noted that in 71% of patients there was appreciable improvement of the eczema, but only scanty follow up data were available.[39]

This study has two important implications. The first is that there may be a case for trying an elemental diet in a child with severely handicapping atopic eczema which has not responded to simpler diets and conventional topical treatment. The need for a further randomised study is clear. The potential hazards of elemental diets, and the need for very close monitoring, indicate that this is an approach that can only be safely undertaken in hospital, with full paediatric and dietetic support. The second implication is that delayed and probably non-IgE mediated eczematous reactions to foods occur in some children with atopic eczema, and merit more detailed and double blind evaluation.

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Baby Check: a scoring system to grade the severity of acute systemic illness in babies under 6 months old

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Abstract

A scoring system has been developed to grade the severity of acute systemic illness in babies under 6 months of age. Data were collected on 28 symptoms and 47 signs from 1007 babies with a spectrum of illness ranging from well to seriously ill. Ordinal regression analysis identified 19 symptoms and signs which in combination graded the severity of the illness most accurately. The coefficients were converted to scores. The higher the score the more serious the illness. When applied to a theoretical cohort of 10 000 babies at home, a score less than 8 has a specificity of 98%, and a score of 13 or more a sensitivity of 92%. The positive predictive value for serious illness increases from zero at a score of zero to approaching 100% at scores over 30. The scoring system has been developed into score cards for parents and professionals.

Parents and doctors recognise when babies are unwell, but they sometimes find it hard to gauge the severity of the illness. Early recognition of serious illness in babies might reduce morbidity and mortality.[1 2] However, there is little information about which are the important signs and symptoms people should be taught to recognise. The preliminary report of the Department of Health and Social Security study of postneonatal mortality suggested 12 symptoms that warranted medical attention the same day.[3] Unfortunately, most were considered to be too common in the community to be useful predictors of serious illness.[4–7] Valman subsequently suggested four 'undoubtedly sinister' symptoms that warranted a paediatric opinion.[8] A study in general practice suggested that at least two were 'too common in infants at home to be regarded as truly sinister'.[9] Valman said that 'the incidence of sinister symptoms in the community needs to be assessed and objective methods of assessing serious illness taught'. A recent House of Commons report reinforced this view.[10]

In companion papers we have presented information about individual symptoms and signs in babies under 6 months old.[11 12] They show that many symptoms and signs in seriously ill babies also occur in babies who are mildly ill. A few individual symptoms and signs are seen only in seriously ill babies but these are rare and indicate an advanced stage of illness. Their sole use would mean that many babies would be missed. Furthermore, it would be preferable to recognise that a baby is ill before he exhibits such signs. If less specific symptoms and signs are used to identify seriously ill babies this will increase anxiety and the workload of the family doctor. This paper presents a scoring system that uses a combination of symptoms and signs to grade the severity of acute systemic illness in babies under 6 months old. The study design and details of the statistical analysis have been reported elsewhere.[13]

Methods

NUMBERS OF BABIES REQUIRED FOR THE STUDY

Accurate determination of the symptoms and signs associated with serious illness requires the rarest to be recorded at least five times.[14] A study in the community would need to enrol about 30 000 babies to ensure this. The only practical way to collected data from seriously ill babies was to enrol them when they presented to hospital, where the incidence of serious illness is much higher than at home. At least 600 were needed to ensure that the rarest symptoms and signs were recorded at least five times. At home, 300 babies were sufficient to quantify the incidence of all but the rarest symptoms and signs.

ENROLMENT OF BABIES

During one year 298 randomly selected full term babies were enrolled postnatally in Cambridge and seen at home evenly across postnatal age (1–25 weeks) and seasons. During the same period 709 babies under 26 weeks old presenting to hospital with an acute problem were enrolled: 27 in Cambridge and 682 at the Royal Children's Hospital, Melbourne (RCH). The RCH assesses a large number of babies with a wide variety of problems because it acts as a primary care centre for the local population.

THE ASSESSMENT

Each mother was asked about 28 predefined symptoms,[11] their duration and her impression of the severity. Only symptoms present in the preceding 24 hours were recorded. Some were clarified with additional questions. The baby was then examined for 47 physical signs.[12 15] The two observers (AJT and PHH) used an identical history questionnaire and examination procedure and practised the assessment to minimise interobserver error. At the end of the study they compared notes to look for systematic differences. As a result two signs, mottling of the skin and mucousy breathing, were found to have been assessed differently and were excluded from further analyses.

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GRADING THE SEVERITY OF ILLNESS

The aim of this study was to grade systemic illness. As there is no 'gold standard' for this it was graded subjectively by the assessors into well, mildly ill, moderately ill, or seriously ill. For comparison each baby's illness was also graded, where possible, using other criteria: positive investigation results (n=200), a review of the notes by three independent paediatricians (n=248), and investigation results (n=682). All the babies were also followed up for three days to ensure no serious diseases had been missed. After comparing each of these criteria, the assessor's impression of the illness was chosen as the grading for subsequent analyses because it was recorded for all babies at the time they were seen, and there was a high level of concordance between this and the independent paediatrician's review ($\kappa=0{\cdot}62$, $p<0{\cdot}001$).[16 17] This level of agreement is similar to other studies comparing clinical judgment.[18 19]

EXPLORATORY ANALYSES

Details of the statistical analysis of this study are reported in full elsewhere.[13] Exploratory analyses showed that symptoms best discriminated illness severity if they were present only during the preceding three days. Continuous variables were investigated as linear and quadratic trends. Most, including respiratory rate, pulse rate, weight, and weight change did not contribute to the prediction of illness severity in the presence of other variables. Two exceptions were rectal temperature and vomiting. These were converted to present/absent variables using the cut offs >38·2°C and 'vomits of at least half the feed after each of the last three feeds'.

IDENTIFICATION OF THE BEST COMBINATION OF SYMPTOMS AND SIGNS FOR GRADING ILLNESS

Logistic and ordinal regression analyses were used to identify the best combination of symptoms and signs to differentiate the three illness groups (well plus mildly ill, moderately ill, and seriously ill).[20 21] The regression coefficient for each symptom and sign represents the increased chance of a baby being ill when that symptom or sign is present. Thus compared with an asymptomatic baby, the chance of a symptomatic baby being ill is the sum of the coefficients for the symptoms which are present. The regression coefficients were converted to integers by multiplying by 3·93 to make a manageable score.[22] The total score could then be calculated for each baby by identifying which of the 19 symptoms and signs the baby had, and adding the corresponding scores.

THE SCORES IN A THEORETICAL COMMUNITY POPULATION

The sample was weighted towards hospital babies. To find the scores likely to occur in the community, a theoretical cohort of 10 000 babies was calculated by taking the babies seen at home as 98% of the population and those seen in hospital as 2%. These proportions were based on the assumption that the hospital babies represented the illest 2% of the population.

SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES

The scoring system is designed to grade the severity of a baby's illness, with increasing scores identifying sicker babies. Specificity (the accuracy with which the score identifies well or mildly ill babies) and sensitivity (the accuracy with which the score identifies seriously ill babies) are calculated for groups of scores as an illustration of the accuracy of the scoring system. Predictive values (the chance of a baby with a given score having a given grade of illness) are shown for individual scores.

Results

Of the 1007 babies, 298 were seen at home and 709 in hospital, of whom 180 were admitted and 529 sent home; two admitted babies died. The assessors' impressions of the babies' illnesses were: 290 well, 305 mildly ill, 247 moderately ill, and 165 seriously ill, of whom nine needed resuscitation.

Of the babies at home 290/298 (97%) were well or mildly ill. None was considered to be seriously ill (table 1). Of the babies presented to hospital 165/709 (23%) were seriously ill, 239/709 (34%) moderately ill, and 305/709 (43%) well or mildly ill. They had a wide range of conditions—for example, upper respiratory tract infection (n=81), lower respiratory tract problems (n=135), diarrhoea and vomiting (n=64), feeding problems (n=20), apnoea (n=16), colic (n=27), intussusception (n=11), meningitis (n=10), urinary infections (n=16), and eczema and dermatitis (n=92).

THE SCORE CARD

Table 2 shows the seven symptoms and 12 signs that in combination graded illness severity best. They are presented as the elements of the score card, called Baby Check, for use by doctors and nurses. The complete version includes definitions, instructions, caveats, and information about interpretation of the score. A booklet for parents has also been produced using identical symptoms, signs, and scores but with more

Table 1 Numbers of babies in each illness category by score group and location

	Score groups				
	0–7	*8–12*	*13–19*	*20+*	*All*
Babies seen at home:					
Well or mildly ill	286	3	1	0	290
Moderately ill	3	3	2	0	8
Seriously ill	0	0	0	0	0
Total	289	6	3	0	298
Babies seen in hospital:					
Well or mildly ill	189	77	36	3	305
Moderately ill	47	67	77	48	239
Seriously ill	8	5	26	126	165
Total	244	149	139	177	709
Theoretical cohort of 10 000 community babies, weighted 98:2 home:hospital:					
Well or mildly ill	9459	120	43	1	9623
Moderately ill	112	118	87	14	331
Seriously ill	2	1	7	36	46
Total	9573	239	137	51	10 000

Table 2 The Baby Check score card. The combination of symptoms and signs shown by regression analysis to predict most significantly the severity of illness

	Score	*p Value*
Score each item according to the exact wording of the question. Only score if an item is definitely present. The baby can be rescored at any time to assess changes in severity of the illness		
Ask about the presence of these symptoms in the last 24 hours:		
(1) Has the baby vomited at least half the feed after each of the last three feeds?	4	<0·001
(2) Has the baby had any bile stained (green) vomiting?	13	<0·01
(3) Has the baby taken less fluids than usual in the last 24 hours?		
If so, score for the *total amount of fluids* taken as follows:		
Taken only slightly less than usual (more than two thirds of usual intake)	3	<0·001
Taken about half the usual amount (between one third and two thirds of usual intake)	4	<0·0001
Taken very little (less than one third of usual intake)	9	<0·0001
• If breast fed ask mother to estimate the amount taken		
• Fluids that have been vomited should still be scored		
(4) Has the baby passed less urine than usual?	3	<0·01
(5) Has there been any frank blood mixed with the baby's stools?	11	<0·001
• Do not score for streaks		
(6) Has the baby been *drowsy* (less alert than usual) *when awake?* If so, score for the degree of drowsiness *when awake,* as follows:		
Occasionally drowsy (but *usually* alert)	3	<0·01
Drowsy most of the time (*occasionally* alert)	5	<0·001
Drowsy all the time (*never* alert)	5	<0·001
• Ensure that mother is reporting drowsiness and not just irritability or increased sleeping		
(7) Has the baby had an unusual cry (sounds unusual to mother)?	2	<0·01
Now examine the baby awake:		
(8) Is the baby's muscle tone reduced?	4	<0·0001
• Compare tone and head control to normal for baby's age		
(9) Talk to the baby. Is the baby concentrating on you less than you would expect?	4	<0·05
(10) Is the baby wheezing on expiration?	3	<0·05
• Do not score for snuffles or upper respiratory noises		
(11) Is the baby responding to what is going on less than you would expect?	5	<0·05
Now undress the baby and examine the baby naked:		
(12) Is there any indrawing (recession) of the lower ribs, sternum or upper abdomen?		
If so, scores as follows:		
Mild recession (*slight* indrawing, just visible)?	4	<0·0001
Moderate recession (*obvious* indrawing, clearly visible)?	15	<0·0001
Severe recession (*deep* indrawing)?	15	<0·0001
(13) Is the baby very pale or does the parent think that the baby has looked very pale in the last 24 hours (*ask the parent*)?	3	<0·0001
(14) Is the baby peripherally cyanosed?	3	<0·05
(15) Squeeze the baby's big toe firmly for 2 seconds to make it white. Release and observe colour return for 3 seconds. Score if return is *not complete* within 3 seconds, or if toe was *completely white to start with*	3	<0·01
(16) Has the baby got an inguinal hernia?	13	<0·0001
• 60% of babies with an inguinal hernia develop complications		
(17) Has the baby an obvious generalised truncal rash or a raw or weeping rash covering an area greater than 5 cm×5 cm?	4	<0·001
(18) Is the baby's rectal temperature 38·3°C or more?	4	<0·001
(19) Has the baby cried during this assessment (more than just a grizzle)?	3	<0·0001
Total score		

The scores are derived from the regression coefficients of the final ordinal regression analysis. These were converted to manageable integers using a factor of 3·93.[22] The p values show the statistical significance of each item in the analysis. The p values would not be shown on the score card.

detailed descriptions, appropriate illustrations, and information.

PREDICTIVE VALUES OF THE SCORES

Table 3 shows the predictive values of a baby having each grade of illness at different scores. The values were derived from curves fitted to the data. The predictive value for serious illness increases from near zero at low scores to nearly 100% for scores over 30. The predictive value for moderate illness is low at low scores, rising to a peak at a score of 16 and falling to zero at high scores. For babies scoring over 16, the chance of having a moderate or serious illness is at least 80%. The risk of serious illness rises steeply for scores over 10. The higher the score the greater the chance of a serious illness.

SCORE GROUPS

The specificity and sensitivity of different score cut offs were explored using Receiver Operating Characteristic curves. Scores of 8 and 13 were identified as the most appropriate lower limits to define moderate and serious illness respectively. A score of 20 defines a group at very high risk of serious illness. The score groups are

Table 3 The predictive values of a baby being well or mildly ill, moderately ill, or seriously ill at different scores

Score	*Well or mildly ill* (%)	*Moderately ill* (%)	*Seriously ill* (%)
0	99	1	0
2	90	9	1
4	85	14	1
6	77	21	2
8	66	30	4
10	54	41	5
12	41	51	8
14	30	58	12
16	20	62	18
18	13	62	25
20	8	58	34
22	5	50	45
24	3	41	56
26	2	32	66
28	1	24	75
30	0	17	83
32	0	12	88
34	0	8	92
36	0	5	95
38	0	3	97
40	0	2	98
42	0	1	99
44	0	1	99
46	0	1	99
48	0	0	100

The three grades of illness are defined as: well or milldly ill=unlikely to need medical attention at present; moderately ill=needs to be seen and assessed. Should be watched closely and probably reviewed; and seriously ill=needs urgent assessment. Probably needs admitting to hospital.

The table can be used to assess the chance of a baby with a given score having each grade of illness. For example, a baby with a score of 24 would have a 3% chance of being well or mildly ill, a 41% chance of being moderately ill and a 56% chance of being seriously ill.

interpreted for parents as: score 0 to 7: 'Your baby is well or only a little unwell and is not likely to need medical attention at the moment.' Score 8 to 12: 'Your baby is unwell, but is not likely to be seriously ill. Contact your doctor, health visitor or midwife for advice. Watch your baby closely, if you think your baby is getting worse do the score again'. Score 13 to 19: 'Your baby is ill and needs to be seen by a doctor. Contact your doctor now and arrange for your baby to be seen'. Score 20 or more: 'Your baby may be seriously ill and needs to be seen by a doctor straight away'. Parents are advised to repeat the score if they think the baby is getting worse.

DISTRIBUTION OF SCORES BY ILLNESS GRADE, LOCATION, AND DIAGNOSIS

Table 4 shows the score centiles for the grades of illness for babies seen at home and in hospital, for babies admitted and sent home, and some common diagnoses.

SCORES FOR BABIES AT HOME

Of the 298 babies seen at home, six (2%) scored between 8 and 12 and three (1%) scored 13 or more, the highest 16. Thus if the mothers had scored the babies at the time, 2% would have been encouraged to get non-urgent medical advice and 1% urgent advice (table 1). If the scoring system were used widely in the community a score of 20 or more would occur in 51/10 000 (0·5%) babies, of whom 36/51 (71%) would be considered seriously ill and 14/51 (27%) moderately ill; only 1/51 (2%) would be well or mildly ill.

SCORES FOR BABIES IN HOSPITAL

One hundred and forty four (80%) of the babies admitted to hospital scored 13 or more. All the babies with life threatening illnesses such as meningitis or intussusception scored over 20. Table 4 shows the median, 10th, and 90th centiles of the score for some common diagnoses.

Table 4 Distribution of scores for babies with different grades of illness, in different locations, and for several diagnoses

	No of babies	Centiles for the scores		
		10	50	90
Grade of illness:				
Well	290	0	0	6
Mildly ill	305	0	6	13
Moderately ill	247	6	13	23
Seriously ill	165	13	29	41
Location:				
Seen at home	298	0	0	5
Seen in hospital	709	3	11	30
Hospital sent home	529	3	9	20
Hospital admitted	180	7	25	41
Diagnosis:				
Conjunctivitis	18	0	4	8
Upper respiratory tract infection	81	3	8	20
Lower respiratory tract infection	74	4	13	24
Diarrhoea and vomiting	64	4	13	30
Hernia	12	11	24	34
Bronchiolitis	51	11	25	41
Intussusception	11	21	31	51
Meningitis	10	20	32	44

SPECIFICITY AND SENSITIVITY

Table 1 shows the number of babies with eacl grade of illness with scores in the ranges 0–7 8–12, 13–19, and 20 and above at home, i hospital, and in a theoretical community population of 10 000 babies.

The specificity of a score between 0 and 7 t identify well or mildly ill babies was lower i babies seen in hospital (189/305, 62%) than a home (286/290, 99%). The specificity for th theoretical community cohort was 9459/962 (98%). Thus the false positive rate for well o mild illness when used in the community woul be about 2%.

The sensitivity of a score of 13 or more t detect a seriously ill baby was 152/165 (92%) giving a false negative rate of 8%. The sensitivity was unchanged for the theoretical community cohort, 43/46 (93%).

FALSE NEGATIVE SCORES

The 8/165 (5%) babies considered to b seriously ill who had scores of less than 8 ha diagnoses of gastro-oesophageal reflux (n=3 and one case each of unusual head nodding convulsion, severe skin rash, early osteomyelitis, and a fractured skull. A further 5/165 (3% graded as seriously ill had scores between and 12. Their diagnoses were enterovirus infection, renal abnormality, screaming (no diagnosis found), acyanotic heart disease (not in hear failure), and a fractured arm. All these babie either had an obvious problem that neede medical attention, or were not seriously ill.

In the community only 2/9573 (0·02%) babie with low scores (0 to 7) would be considered t be seriously ill.

FALSE POSITIVE SCORES

Three babies assessed as well scored 13, 13, an 17, and 37 babies rated as mildly ill scored 13 o more (five scored more than 17). Review of th case histories and diagnoses suggested that th scores gave a reasonable impression of eacl baby's illness—that is, they needed to be assessed by a doctor.

MOTHERS' IMPRESSION OF THE ILLNESS COMPARED WITH THE SCORE

For babies seen in hospital the mother's gradin of the baby's illness was compared with that o the assessor. The mothers graded 474/709 (67% babies as moderately or severely ill compare with 404/709 (57%) graded as such by the assessor. The concordance was poor ($\kappa=0{\cdot}26$). Th mothers' grading of moderate or serious illnes had a positive predictive value of 66% and negative predictive value of 62%. The scorin system using a cut off of 13 or more gave a positive predictive value of 88% and a negative predictive value of 68%. The score was therefor more accurate at grading illness than th mothers.

Discussion

Paediatricians use their clinical judgment to sif rapidly through many symptoms and signs to assess whether a baby is seriously ill. The scoring system presented in this paper has distilled the 19 factors that in combination can simulate the assessment of one experienced paediatrician (PHH). It is therefore a systematised version of his personal judgment. There was reasonable concordance between PHH and the independent paediatricians, suggesting that the 19 items also reflect their judgment. The significance levels of the 19 symptoms and signs shown in table 2 suggest that if the study were repeated most of the factors would still be identified as important. Use of the score card should enable parents and family doctors to give a grade to the illness severity similar to that of the original paediatrician.

The study data came from two centres, each with its own observer and prevalence of illness. This may have affected the 19 symptoms and signs identified. However, this difficulty has been considered during the analysis. In addition to the results presented in the combined data, separate analyses were carried out on the Melbourne data alone to remove the interobserver effect. The results were very similar, with the same combination of symptoms and signs being identified, although there were differences in the values of the scores, reflecting the inclusion of a large number of well babies in the combined data set. The similarity of the results suggests that illness severity rather than any difference between the two observers or centres was the reason the individual symptoms and signs were selected.

Although the prevalence of disease in the two centres was different, the signs and symptoms associated with specific conditions such as bronchiolitis were the same. Thus the combination of symptoms and signs should be useful for grading illness anywhere.

A scoring system to be used by inexperienced people must not miss serious illness. The 8% false negatives either had conditions that would not have been considered serious by other observers, or would have been recognised from other features (for example, a swollen immobile arm in the case of osteomyelitis).

The score assesses the severity of acute systemic illness. Some conditions, such as a convulsion, obviously need medical attention but may get a low score if the baby is not systemically ill. In most cases a score is not needed to assess such conditions. If there is any doubt, however, the score can still be used to show the level of systemic illness. For example, a baby with a fit may score 0 if generally well, or 30 if it has meningitis. The score card includes specific information about conditions which need medical care but which score low. The scoring system is not a substitute for common sense or experience, rather it is a tool to help people quantify the severity of an illness.

The score grades the illness at the time it is done and can be repeated to assess whether the baby is getting better or worse.

If the scoring system were to be used at home it would probably not increase the number of mothers seeking medical attention. In this study it would have encouraged 1% to seek urgent attention and 2% non-urgent advice. In fact 3% had seen the doctor on the day of the assessment and two babies were under review.[11] An unrecorded number had also seen the midwife or health visitor. Babies at home who scored less than 8 were very likely to be considered well or mildly ill. Thus the score card should give mothers confidence not to seek medical advice. It could also encourage them to seek urgent medical advice appropriately if their baby had a high score.

Some symptoms and signs that might be considered important were not selected for the score card. This was because either they were very uncommon, or other factors in combination were better at differentiating the illness, or their addition did not significantly improve the accuracy of the score.

Some people might be unhappy about mothers measuring rectal temperature. A digital thermometer is provided with the mother's score card. It has a rounded end 3 mm in diameter and a flange to prevent insertion too far into the rectum. Illustrations show how it should be used. Our experience, and that of others,[23] is that mothers can safely measure rectal temperature.

This scoring system is the most accurate system for grading acute systemic illness we could devise. Although it would be desirable to have a simple check list of a few individual symptoms and signs[15] it would not grade the illnesses as accurately, nor be so sensitive or specific as the Baby Check system, which uses a weighted combination of symptoms and signs.

It is important to find out how the score card works in practice, whether or not people can use it and find it useful, and how accurate it is in different situations. These issues have been studied in field trials, the results of which are reported in companion papers.[24–27]

In conclusion, the Baby Check scoring system using a combination of 19 symptoms and signs appears to be a highly sensitive and specific tool which should be useful to help quantify the severity of a baby's systemic illness.

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Copies of the Baby Check score card and booklet can be obtained from the authors.

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NOWCA

Some small babies get into alarming difficulty with nasal obstruction or snuffliness. Reference to standard paediatric texts for guidance on the management of this problem is singularly unhelpful. Perhaps the first step is to have a name for the problem so that we can recognise it and talk about it. Derkay and Grundfast in a welcome paper (*International Journal of Pediatric Otorhinolaryngology* 1990;**19**:241–9) call it NOWCA (nasal obstruction without choanal atresia). They describe 15 babies aged between 1 week and 8 months seen in Washington DC. Methods of assessment included fibreoptic and rigid tube endoscopy, computed tomography of the nose, and sleep studies with measurement of heart rate, chest wall movement, nasal or tracheal air flow, and oxygen saturation by pulse oximetry. Of the 15 babies four had oedema of the nasal mucosa, three each had isolated choanal stenosis, choanal stenosis with other craniofacial anomalies, and adenoid obstruction, and two had congenital syphilis.

Therapeutic measures included insertion of a nasopharyngeal airway, steroid nose drops, adenoidectomy, and home cardiorespiratory monitoring after teaching parents about resuscitation. Twelve of the babies were well by 6 months of age and the other three by 9 months.

I suspect that this is a fairly common problem that we've been slow to latch on to, though I don't expect to see many caused by congenital syphilis. The next time you see your friendly ear, nose, and throat surgeon say 'NOWCA' and if he doesn't respond hit him about the head with this paper.

ARCHIVIST

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Field trials of the Baby Check score card: mothers scoring their babies at home

A J Thornton, C J Morley, S J Green, T J Cole, K A Walker, J M Bonnett

Abstract

The Baby Check score card has been developed to help parents and health professionals grade the severity of acute illness in babies. This paper reports the results of two field trials in which mothers used Baby Check at home, 104 mothers scoring their babies daily for a week and 56 using it for six months. They all found Baby Check easy to use, between 68% and 81% found it useful, and 96% would recommended it to others. Over 70% of those using it daily used it very competently. Those using it infrequently did less well, suggesting that familiarity with the assessment is important. The scores obtained show that Baby Check's use would not increase the number of mothers seeking medical advice. With introduction and practice most mothers should be able to use Baby Check effectively. It should help them assess their babies' illnesses and make appropriate decisions about seeking medical advice.

Parents recognise when their baby is unwell, but they may have difficulty assessing the severity of the illness and deciding on appropriate management.[1-3] 'Baby books' describe specific diseases, but do not help parents assess illness severity. Advice about when to call a doctor is often vague.

Baby Check is a score card developed to help parents and health professionals grade the severity of acute illness in babies under 6 months old.[4 5] It contains 19 simple checks (seven symptoms and 12 signs), each carrying a score. The scores for positive checks are added together. The higher the total score, the sicker the baby.

The 19 checks as described for professionals are summarised in a companion paper.[4] For parents, an illustrated booklet has been developed. Each check is explained in simple language (for example, reduced tone is described as 'floppiness'; recession as 'sucking in the rib cage'). Figure 1 shows examples of two checks. The total score is divided into four groups: 0 to 7, 8 to 12, 13 to 19, and 20 or more. Advice is given about what to do when the baby's score falls into each (see table 1).[4] Other information is included about important conditions which give low scores, what to do if the baby is getting worse, and how to get medical help.

For Baby Check to be accepted for mothers' use, the majority should find it easy, be able to use it competently, and react appropriately to its guidance. The scores mothers obtain should be reliable when compared with those of a trained observer, and accurately reflect illness severity. General practitioners need reassurance that well babies do not obtain falsely high scores.

This paper reports the results of two field trials in which mothers used Baby Check at home.

Subjects and methods

STUDY A: MOTHERS SCORING BABIES AT HOME DAILY FOR ONE WEEK

The study involved 104 mothers of term babies, randomly selected from the birth register. They were approached postnatally and asked to score their babies daily for a preallocated week and to record contacts with their doctor, health visitor, or midwife. Babies were assessed uniformly across the first six months of life.

The mothers received no instructions other than those in Baby Check, which was posted to them shortly before they started scoring. They were told it was a research project and that they should not rely on it when deciding whether to contact a doctor. At the end of the week a research nurse visited, watched the mother score her baby, graded her competence in using Baby Check, questioned her about it, and then scored the baby herself.

Of the 104 participants, 72 (69%) were the original mothers approached and 32 (31%) were substitutes for mothers who refused.

STUDY B: MOTHERS USING BABY CHECK AT HOME FOR SIX MONTHS

Seventy mothers of term babies born on selected days were invited to take Baby Check home to use whenever they wished, until their baby was 6 months old. They were given no additional instructions in its use. They were advised that it was a research project. A research nurse visited when the babies were 8 (visit 1) and 16 weeks' old (visit 2). The procedure for each visit and for recording medical contacts was as in study A. The mothers received a questionnaire about Baby Check at the end of six months.

Sixty seven (96%) of the mothers approached agreed to participate, but 11 subsequently withdrew. Fifty five were seen at each visit, but one did not score her baby at visit 2. Fifty (89%) of the 56 questionnaires were returned.

Table 2 shows the mothers' social class and educational qualifications.

Statistical analyses were performed with SPSSX, using correlations, paired and unpaired *t* tests.

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Unusual cry

You will be used to your baby's normal cries (from hunger, tiredness, etc). An unusual cry is different.
It may be weak, hoarse, high pitched or painful for example.

If your baby's cries have been normal in the last 24 hours: **Score 0**

If your baby has been crying in an unusual way in the last 24 hours: **Score 2**

Score for one box only.

Circulation

This check is about how well your baby's blood is circulating to the fingers and toes.
Squeeze your baby's big toe firmly for two seconds, to make a white patch.
(To time two seconds count: 'One squeeze the toe, two squeeze the toe'). Then let go and count three seconds.
Watch how quickly the colour returns.

If your baby's toe returns to its normal colour within three seconds: **Score 0**

If your baby's toe does not return to its normal colour within three seconds, or was completely white to start with: **Score 3**

Score for one box only.

Figure 1 Examples of how the checks are described.

Table 1 Summary of advice given to parents for each score group

Score	*Advice*
0 to 7	Your baby is well or only a little unwell and is not likely to need medical attention at the moment
8 to 12	Your baby is unwell but is not likely to be seriously ill at the moment. Contact your doctor, health visitor, or midwife for advice. Watch your baby closely. If you think your baby is getting worse, do the score again
13 to 19	Your baby is ill and needs to be seen by a doctor. Contact your doctor now and arrange for your baby to be seen
20 or more	Your baby may be seriously ill and needs to be seen by a doctor straight away

Table 2 Mothers' social class and educational qualifications. Results are number (%)

	Study A (n=104)	*Study B (n=56)*
Social class:		
I	27 (26)	8 (14)
II	21 (20)	13 (23)
III Non-manual	4 (4)	—
III Manual	34 (33)	21 (38)
IV	8 (8)	3 (5)
V	5 (5)	5 (9)
Other	4 (4)	6 (11)
Not coded	1 (1)	—
Mother's educational qualifications:		
No qualifications	15 (14)	10 (18)
≤4 CSEs/hairdressing/typing	11 (11)	9 (16)
>4 CSEs/any O levels	36 (35)	17 (30)
A levels/vocational training	12 (12)	4 (7)
Degree/professional qualification	24 (23)	16 (29)
Not coded	6 (6)	—

Table 3 Checks reported as difficult. Results are number (%)

Check	*Study A (n=104)*	*Study B*	
		Visit 1 (n=55)	*Visit 2 (n=54)*
Recession	25 (24)	11 (20)	3 (6)
Rectal temperature	7 (7)	3 (5)	—
Reduced fluids	5 (5)	3 (5)	1 (2)
Hernia	3 (3)	4 (7)	1 (2)
Circulation	3 (3)	3 (5)	1 (2)

Recession was also reported twice on the final questionnaire (study B).
The remaining checks were reported as difficult on three occasions or less.

Results

THE NUMBER OF TIMES THE MOTHERS USED BABY CHECK

In study A, 701 (96%) of 728 possible daily scores were completed.

In study B, 33 mothers (59%) used Baby Check spontaneously between visits, 13 (23%) once, eight (14%) two to four times, and 12 (22%) five times or more.

MOTHERS' IMPRESSIONS OF BABY CHECK

Ease of use

All the mothers rated Baby Check as easy to use in study A. In study B all but two (4%) thought it easy at visit 1. All thought it easy at visit 2.

Difficult checks

Most mothers did not find any checks difficult. Thirty six (35%) mentioned difficulties in study A, 21 (38%) in study B at visit 1, and seven (13%) at visit 2. In study B the better educated mothers were the most likely to report checks as difficult ($r=0{\cdot}52$, $p<0{\cdot}001$). Only recession, rectal temperature, fluid intake, hernia, and circulation were mentioned by more than three (table 3).

Recession accounted for 41 (43%) of the reports. Mothers were unsure what to look for. When shown a photograph of recession at visit 2, 34 (62%) said they would recognise it from Baby Check's description.

Baby Check requires mothers to take their baby's rectal temperature using the digital thermometer provided. Ten (6%) mothers thought this was difficult, five of whom had not attempted it. Of those who took the temperature, only five (5%) in study A, and none in study B thought it difficult.

Those mothers who found fluid intake difficult to quantify were breast feeding. Those who mentioned hernia were unsure what to look for and with circulation (fig 1) they were unsure about detecting the colour change.

Disliked checks

Rectal temperature was disliked by 41 mothers (39%) in study A. In study B, the number dropped from 22 (40%) at visit 1 to 10 (19%) at visit 2. Reasons included fear of hurting the baby and feeling the check was unnecessary. Most mothers were willing to do the check. In study A, 91 (88%) took the temperature at least once. In study B at visit 1, 36 (67%) did the check (about half requiring persuasion) and 18 (33%) refused. At visit 2, only 10 (19%) refused and fewer needed persuasion.

The circulation check was disliked by two mothers (2%) in study A. Both were afraid of hurting the baby.

Does Baby Check cause anxiety or provide reassurance?

The mothers in study A were asked whether Baby Check caused anxiety or provided reassurance. Forty six (46%) found it reassuring. Only four (4%) said it caused anxiety.

Usefulness

In study A, 75 (74%) mothers thought Baby Check was useful. In study B, 43 (81%) at visit 1, 41 (76%) at visit 2, and 43 (68%) on the final questionnaire thought it useful. All thought other mothers would find it useful and 47 (96%) said they would recommend it.

Eighty four mothers (83%) in study A said they would like a copy of Baby Check and 69 (68%) said they would buy it. In study B (visit 2) the numbers were 45 (87%) and 44 (83%) respectively. First time mothers were slightly more likely to want a copy than those who had other children (r=0·27, p<0·05). On the final questionnaire 38 (76%) said they would like one if they had another baby. Forty (80%) would buy it. On average they were willing to pay £5·75.

Willingness to trust Baby Check

The mothers in study B were asked whether they would trust Baby Check to help them decide when to contact the doctor. At visit 2, 25 (46%) said they would, 19 (34%) would not, and 11 (20%) were unsure. By the end of the study, 32 (64%) said they would, though many said it would not override their own judgment.

MOTHERS' COMPETENCE IN USING BABY CHECK

Table 4 shows the nurse's grading of the mothers' competence in using Baby Check.

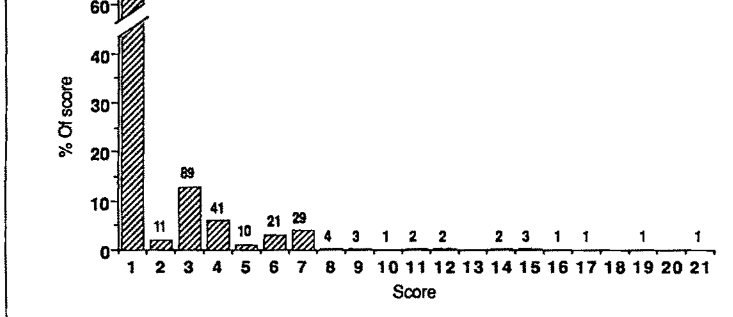

Figure 2 Profile of daily scores (n=701). The number of babies with each score are shown at the top of each column.

Table 4 Mothers' competence in using Baby Check at the nurse's visit. Results are number (%)

Competence grading	*Study A (n=100)*	*Study B*	
		Visit 1 (n=55)	*Visit 2 (n=54)*
Excellent	26 (26)	3 (6)	6 (11)
Good	45 (45)	15 (27)	14 (26)
Reasonable	9 (9)	21 (38)	17 (31)
Dubious	5 (5)	9 (16)	9 (17)
Poor	9 (9)	3 (6)	4 (7)
Very poor	1 (1)	4 (7)	3 (6)
Not gradeed	5 (5)	—	1 (2)

Those whose competence was not graded scored their babies 'from memory', Four mothers in study A, and one at visit 2 in study B did not do an assessment at the visit. The assessment was graded as reasonable or better for 80 mothers (80%) in study A, 39 (71%) at visit 1 and 37 (69%) at visit 2 in study B.

Four mothers (4%) in study A and two in study B made arithmetical errors.

Factors affecting mothers' competence

In both studies, mothers' competence was weakly correlated to social class (r=0·24, p=0·01 and r=0·25, p<0·05), mothers from the manual classes performing slightly less well.

In study B, mothers who had used Baby Check beforehand performed significantly better at visit 1 than those who had not (r=0·5, p<0·001). This effect was absent at visit 2. Mothers with no qualifications (table 2) performed better assessments at visit 1 than those with fewer than four passes at the certificate of secondary education (CSE) (p<0·05). Those with fewer than four CSEs performed significantly less well than the graduate mothers (p=<0·05).

The mothers' age and parity had no significant effect on their competence in using the score card in either study.

PROFILE OF SCORES

Figure 2 shows the profile of daily scores in study A. Of 95 babies with all seven daily scores, 84 (88%) scored less than 8 every day.

Table 5 shows all the mothers' scores, in the four score groups. The scores done between visits in study B were higher than those done routinely in either study.

AGREEMENT BETWEEN THE MOTHERS' AND NURSE'S SCORES

In study B, four assessments from each visit were excluded because the scores recorded by the mother were uninterpretable.

There was no significant difference between the distribution of the mothers' and nurse's total scores. They were identical in 77 (77%) cases in study A, in 32 (63%) at visit 1, and in 38 (76%) at visit 2. The mean (SD) difference between the scores was −0·2 (1·6) in study A, 0·5 (2·5) at visit 1, and −0·1 (2·7) at visit 2. Sixteen mothers (16%) in study A, 12 (24%) at visit 1 and five (10%) at visit 2 scored lower than the nurse, while seven (7%) in study A, and seven

Table 5 Distribution of mothers' scores. Results are number (%)

Score	Study A		Study B		
	Daily (n=701)	*Visit (n=100)*	*Visit 1 (n=51)*	*Visit 2 (n=50)*	*Between visits (n=117)*
0 to 7	680 (97)	97 (97)	49 (96)	48 (96)	97 (83)
8 to 12	12 (2)	3 (3)	1 (2)	1 (2)	10 (9)
13 to 19	8 (1)	—	1 (2)	1 (2)	8 (7)
20 or more	1 (<1)	—	—	—	2 (2)

Table 6 Checks scored differently by the mother and nurse, showing whether the mother scored higher or lower than the nurse. Results are number (%)

Check	Study A (n=100)		Study B			
			Visit 1 (n=51)		*Visit 2 (n=50)*	
	Mother high	*Mother low*	*Mother high*	*Mother low*	*Mother high*	*Mother low*
Crying	1 (1)	9 (9)	6 (12)	5 (10)	—	—
Circulation	2 (2)	7 (7)	—	2 (4)	1 (2)	3 (6)
Recession	1 (1)	1 (1)	3 (6)	2 (4)	—	3 (6)
Rash	—	2 (2)	2 (2)	—	—	1 (2)
Cyanosis	2 (2)	—	1 (1)	1 (1)	—	—
Reduced fluids	—	—	—	1 (2)	2 (4)	1 (2)

The remaining checks were scored differently on three occasions or less.

(14%) at each visit in study B scored higher. The mothers' and nurse's scores fell into different scoring groups in only three cases.

The agreement in scoring of individual checks was between 78% and 100%. The checks which gave rise to most differences are shown in table 6. The differences in the scoring of crying often arose when babies who were content when their mothers assessed them, cried during the nurse's examination. Doing the circulation check, some mothers did not squeeze the toe firmly enough. In seven cases (70%) with differences in the scoring of recession, and in three (60%) where rash was scored differently, the mother did not undress or examine the baby.

MEDICAL CONTACTS

In study A, 10 babies (10%) had 18 contacts with their health visitor, midwife, or doctor, mostly for minor complaints. Six mothers reported that Baby Check had helped them decide whether or not to seek advice; four were reassured by a low score, and scores of 15 and 19 prompted two to seek advice—one baby had a chest infection, the other asthma and a severe cold.

In study B, 53 contacts were recorded. There were also 79 unrecorded contacts reported at the visits. The scores completed between visits were correlated with the recorded contacts. Twenty two (42%) had a score done the same day. A contact was recorded for seven (70%) of 10 scores of 13 or more compared with only seven (7%) of 97 scores below 8.

Discussion

The mothers found Baby Check easy to use, the majority found it useful, and almost all would recommend it to others. Most would like a copy and would be prepared to buy it.

Overall 75% of the mothers used Baby Check at least reasonably well. It study A, 71% used it very competently. In study B they performed less well. Initially more mothers found checks difficult in study B and there was greater disagreement between the mothers' and nurse's scores, but as the study progressed they reported fewer difficulties, the agreement improved and they became more inclined to trust Baby Check and to consider it useful. Familiarity with the assessment is thus important. The booklet is currently being revised, encouraging mothers to practise by scoring their well babies, and to ask their health visitor or midwife about checks that need clarifying. The text and illustrations for the checks causing most difficulty are being improved.

For those mothers who are unable to use Baby Check reliably, it would be possible to devise a simpler check list, based on a few individual symptoms. However such a system would inevitably be much less sensitive and specific. It could thus cause increased anxiety and cause ill babies to be missed.

The mothers' willingness to use and trust Baby Check will have been influenced by its presentation as a research project rather than as a decision aid. They were given no help in its use, whereas in future they could be introduced to it by their health visitor, midwife, or by a video. This should further increase their competence.

The mothers were asked to score well babies. They would usually use Baby Check when the baby was unwell. This may have affected their motivation to complete the assessments properly and to take the rectal temperature. It may also have increased their uncertainty about some checks—many thought they would recognise signs such as recession if present.

The sample was biased towards the higher social classes and professional mothers, but just under half were from manual classes and a third had fewer than four CSEs. The analyses suggest that social class and education have only a marginal effect on mothers' reactions to and competence with Baby Check.

Although not common in this country, mothers take their baby's rectal temperature routinely in Europe. The Baby Check thermometer has a collar to prevent its being inserted too far into the rectum. Most mothers were willing to take the temperature and did so competently. The number who disliked it or thought it difficult fell once they had tried it. The mothers were asked to undertake a new procedure on a well baby without teaching. Their only guidance was that contained in Baby Check. In future health visitors or midwives could show mothers how to take the rectal temperature.

Clinicians assessing signs agree only about 68% of the time.[6] The agreement between the mothers' and nurse's scores was good, provided the mother undressed and examined the baby. Some differences in scoring arose because they did not, and the instructions have since been improved. Differences in the scoring of crying usually reflected the baby's true state. The advice given by Baby Check depends on the scoring group—there were only three cases where the mother's and nurse's scores fell into different groups.

Because there were few ill babies conclusions cannot be drawn about mothers' ability to recognise signs and symptoms when present, but it is important to establish that the mothers do not overscore. When the score was applied to 298 babies seen at home in the original study,[4 5] 289 (97%) scored 0 to 7, six (2%) scored 8 to 12, and three (1%) scored 13 to 19. The profile of scores in these studies is very similar, confirming that well babies assessed by their mothers score low.

Only 11 babies (12%) in study A scored 8 or more during the week. This is fewer than the number who contact their doctor at the moment.[7] Thus if mothers were to use Baby Check, fewer would be encouraged to seek advice than do so currently. Serious illness is uncommon in babies at home, and scores of 20 or more were rare, confirming that babies who achieve them need urgent assessment.[4 5 8 9]

The scores done between visits in study B were higher than those done at the visits, suggesting that the mothers were using Baby Check appropriately when worried about their babies. Mothers often sought advice without using Baby Check (they were told not to rely on it), but those who did use it appear to have responded appropriately. Even allowing for unrecorded contacts, a score under 8 reassured most that medical advice was not required, while few ignored a score of 13 or more.

Many who said they would trust Baby Check qualified their answers. This is appropriate—Baby Check is intended to assist rather than replace the mothers' judgment.

This study has shown that mothers welcome Baby Check, and with introduction and practice most should be able to use it effectively. If it were introduced as part of child care it would not increase, and might reduce, the numbers seeking medical advice. Baby Check should reassure mothers when attention is not required a well as prompting them to seek advice when this is necessary. Their willingness to use it long term will be affected by its presentation, and by whether it becomes an accepted and recommended part of baby care.

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Copies of the Baby Check score card and booklet can be obtained from the authors.

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Field trials of the Baby Check score card in general practice

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Abstract

Sixteen general practitioners (GPs) used the Baby Check score card to assess illness severity in 86 babies under 6 months old. Their reactions to Baby Check were positive: in 79 (92%) it gave an accurate assessment of the baby's illness and 16 (100%) said they would trust it. Fifteen (94%) found it useful, and most of those who did not said the baby was not ill or had an obvious diagnosis. Thirteen (81%) said they would use it and wanted their health visitors and midwives to use it and 15 (94%) wanted the mothers in their practice to use it. The majority (64%) of babies scored 0–7; 31% scored 8 to 19; and only 5% scored over 20. Well babies had low scores, while the two sickest babies, needing urgent hospital treatment, scored 29 and 33. The use of Baby Check by GPs would help them assess babies thoroughly and quantify illness severity objectively.

The assessment of illness in babies in the first few months of life can be difficult for general practitioners (GPs) because many lack paediatric training[1] and most of the babies they see are mildly ill. Many of the symptoms seen in seriously ill babies are also common in babies who are well or mildly ill.[2] Early recognition of serious illness in babies might reduce both morbidity and mortality.[3]

The Baby Check scoring system, presented in companion papers,[4 5] has been developed to help parents, nurses, and doctors quantify the severity of acute systemic illness in babies in the first six months of life. The severity of a baby's illness is assessed using seven symptoms and 12 signs and adding the scores for any which are positive. The higher the total score the sicker the baby.

The health professionals' version of Baby Check contains the 19 checks with definitions, instructions on use, and information about low scoring conditions that still require attention—for example, convulsions or an abscess. It also contains a table showing the chance of a baby with each score being well or mildly ill, moderately ill, or seriously ill.

For parents the scores were divided into four groups: 0 to 7, 8 to 12, 13 to 19, and 20 or more. Table 1 shows the advice given to parents for each score group.

This paper reports a field trial in which GPs used Baby Check when assessing babies presenting with an acute illness.

Table 1 Summary of advice given to parents for each score group

Score	*Advice*
0 to 7	Your baby is well or only a little unwell and is not likely to need medical attention at the moment
8 to 12	Your baby is unwell, but is unlikely to be seriously ill at the moment. Contact your doctor, health visitor, or midwife for advice. If you think your baby is getting worse do the score again
13 to 19	Your baby is ill and needs to be seen by a doctor. Contact your doctor now and arrange for your baby to be seen
20 or more	Your baby may be seriously ill and needs to be seen by a doctor straight away

Methods

One hundred and twenty seven local GPs were invited to participate in the trial: of these 28 agreed. Four others also asked to take part. Each participant was sent a booklet containing 10 score cards and forms for data collection. They were asked to assess babies under 6 months of age who presented with an acute illness. Firstly they had to record their impression of the severity of the baby's illness in four categories: well, mildly ill, moderately ill, and seriously ill. They then scored the baby using Baby Check, after which they graded their final impression of the baby's illness on a seven point scale, which was simplified into four grades for analysis.

After each assessment the GPs answered questions about the usefulness and accuracy of the score. At the end of the study a questionnaire asked for their impressions of the system. They were given no additional instructions about its use so that the field trial could assess Baby Check as it might be used in general practice.

Results

Of the 32 GPs in the field trial 17 completed 94 assessments. Eight of these had to be excluded because the doctor misunderstood the score card.

QUESTIONS ASKED AFTER EACH ASSESSMENT

Was Baby Check helpful?

An answer was recorded for 78 cases. In 58 (74%) Baby Check was found helpful. In 20 (26%) it was not particularly helpful because the baby was clearly not ill or had an obvious diagnosis: thus a Baby Check assessment and score was not required. In one case the GP was worried that a temperature of 38·1°C was not reflected in the score.

Did you miss out any checks?
Rectal temperature was omitted in 12 (14%) assessments, seven because the assessor did not have a thermometer. In five they thought it was unnecessary. In four (5%) they forgot the big toe squeeze.

Were any of the checks difficult or unclear?
Checks were reported as being difficult in six (7%) cases. Concentration was difficult in two because the baby was either crying or had his eyes closed. Awareness, drowsiness, cyanosis, unusual cry, and temperature were each mentioned once.

QUESTIONS ASKED AT THE END OF THE TRIAL
Is Baby Check useful for assessing illness in babies?
Fifteen GPs (94%) said it was useful. The other one felt his own judgment and the family history were more important.

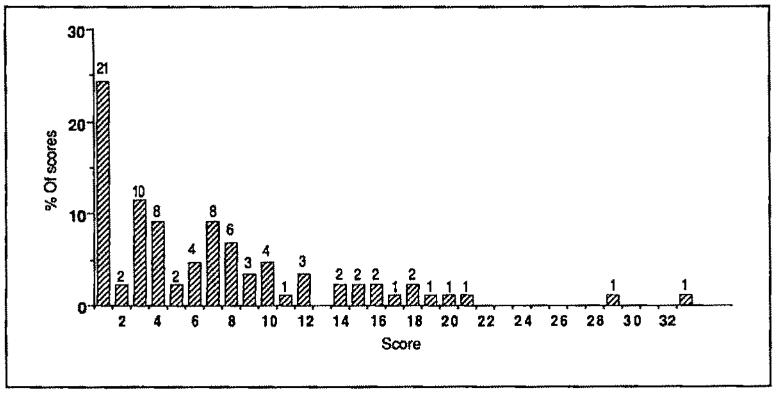
Would you trust Baby Check as an indicator of illness severity?
All said yes.

Would you like to use Baby Check if it became available?
Thirteen (81%) said yes. Two (13%) said they might use it occasionally. One (6%) said he would rely on his own judgment.

How would you use Baby Check?
Of the 13 (81%) who said they would use it, five (38%) would use it for all consultations about acute illness and eight (62%) only when they thought the baby was at risk of serious illness.

Would you like your health visitors and midwives to use Baby Check?
Thirteen (81%) said yes.

Would you like the parents in your practice to use Baby Check?
Fifteen (94%) said they would like their parents to use it.



Profile of scores (n=86). The number of babies within each score are shown at the top of each column.

Table 2 Scores thought to be too high or too low

Score thought to be too high:
(1) Scored 9. Diagnosed as having thrush. Given a prescription
(2) Scored 18. The examination revealed a hernia, but the general practitioner felt this was not causing any problems
(3) Scored 29. Admitted to paediatric intensive care, diagnosed congenital adrenal hyperplasia

Score thought to be too low:
(1) Scored 7. A 'happy wheezer'. General practitioner thought the score did not represent the level of risk because the mother was exhausted and the social circumstances were poor
(2) Scored 6. Jaundiced baby, 11 days old, weighed less than birth weight. Referred to hospital but not admitted
(3) Scored 11. Referred to hospital but not admitted. Diagnosis of otitis media
(4) Scored 2. Mother reported the baby had difficulty breathing. No treatment given

GP'S OPINION OF THE ACCURACY OF THE SCORE CARD
The GPs were asked whether they thought the score gave an accurate assessment of the baby's illness. In 79 of the 86 assessments (92%) they said that it did, in three (3%) they thought the score was too high for the severity of illness and in four (5%) they thought the score was too low for the severity of illness. These cases are shown in table 2.

SCORES RELATED TO THE SEVERITY OF ILLNESS
The percentage of the babies with each score is shown in the figure. The distribution of babies in the four score groups was: 55 (64%) scored 0 to 7, 17 (20%) scored 8 to 12, 10 (12%) scored 13 to 19, and four (5%) scored 20 or more. The GPs' initial impression of the severity of the babies' illness before they did the Baby Check score, and their final grading are shown in tables 3 and 4 correlated with the score groups. The scores of babies with different diagnoses are shown in table 5.

Babies scoring 0 to 7
Of the 55 babies in this group, the initial impression was that 51 (93%) were well or mildly ill. The diagnoses made were: upper respiratory tract infection (n=25), well (n=9), viral infection (n=4), mild gastroenteritis (n=3), conjunctivitis (n=2), rash (n=2), otitis media (n=2), thrush (n=1), umbilical sepsis (n=1), 'happy wheezer' (n=1), and feeding problem (n=1). Three (5%) were considered to be moderately ill, their diagnoses were: a feeding problem, an upper respiratory tract infection, and breast milk jaundice. None was considered to be seriously ill. One was not graded.

Table 3 Initial impression of illness severity correlated with the score groups

Illness severity	*Score groups*			
	0 to 7	*8 to 12*	*13 to 19*	*20 or more*
Well	20	0	1	0
Mildly ill	31	14	4	2
Moderately ill	3	2	5	2
Seriously ill	0	0	0	0

The initial impression was not recorded for two babies.

Table 4 Final grading of the illness severity correlated with the score groups

Grade of illness severity	*Score groups*			
	0 to 7	*8 to 12*	*13 to 19*	*20 or more*
(1) Has a serious illness needing hospital treatment	0	0	1	2
(2) Requires hospital admission for observation due to uncertainty about the severity of the illness	1	1	0	0
(3) Needs careful observation and treatment. Could be managed at home by a capable mother	5	4	6	1
(4) Mildly ill or well. Could be managed at home by any mother	49	12	3	1

Table 5 Diagnoses and scores

Diagnosis	*No of babies*	
		Median (range) score
Upper respiratory tract infection	31	3 (0 to 12)
Well and minor problems	14	0 (0 to 4)
Viral infection	14	10 (0 to 21)
Bronchiolitis/bronchitis	6	13 (4 to 33)
Gastroenteritis	6	6 (3 to 19)
		Individual scores
Otitis media	4	4, 6, 11, 12
Conjunctivitis	4	0, 0, 8, 20
Thrush	3	0, 4, 9
Adrenal hyperplasia	1	29
Inguinal hernia	1	18
Umbilical infection	1	7
Jaundice	1	6

At the final grading 49 (89%) were considered to be well or only mildly ill (grade 4). One (2%) was referred to hospital (grade 2) because his parents were worried as a sibling had died from a respiratory infection, and five (9%) were considered to need careful observation (grade 3).

Babies scoring 8 to 12

Of the 17 babies in this group the initial impression was that 14 (82%) were mildly ill. The diagnoses made were: upper respiratory tract infection (n=8), viral infection (n=2), gastroenteritis (n=1), thrush (n=1), conjuctivitis with jaundice (n=1), bronchiolitis (n=1). Two (12%) were moderately ill. Their diagnoses were upper respiratory tract infection and otitis media. One was not graded.

At the final grading, 12 (71%) were graded 4 and four others (24%) were graded 3; one (6%) with otitis media was considered to need hospital observation (grade 2) and was seen but not admitted.

Babies scoring 13 to 19

Of the 10 babies in this group, the initial impression was that one (10%) was well, having presented with crying all night. He was found to have an inguinal hernia when examined. Four (40%) were mildly ill and the diagnoses made were: gastroenteritis, viral infection, bronchiolitis, and vomiting. The other five (50%) were moderately ill and the diagnoses made were: viral infection (n=2), gastroenteritis (n=2), and upper respiratory tract infection (n=1).

At the final grading, three (30%) were graded 4, six (60%) were graded 3, and the baby with a hernia was considered to need hospital treatment (grade 1).

Babies scoring 20 or more

Of the four babies in this group, none w thought to be well. Two (50%) were mildly i one diagnosed as having an upper respirato tract infection with conjunctivitis and the oth a viral infection. Two (50%) were moderate ill. Their scores were 29 and 33. The fin diagnoses made were congenital adrenal hype plasia and bronchiolitis. At the final gradin one was graded 4 and one as grade 3. The babi scoring 29 and 33 were admitted to hospi urgently (grade 1) and the one with congeni adrenal hyperplasia received intensive care.

Discussion

The data were obtained from a small number GPs and therefore must be interpreted with ca tion. Nevertheless, a number of useful poi emerge. Their reactions to Baby Check we mainly positive: in 74% of cases they found helpful, 100% would trust it, 81% said th would like to use it, 81% said they would li their health visitors and midwives to use it, a 94% said they would like parents in their pra tice to use the parents' version.

There were no objective criteria by which judge whether the diagnoses, treatment, a scores were correct. In consequence we ha not been able to present the sensitivity a specificity of the scores. To determine wheth the scores accurately graded the severity the babies' illnesses they were compared wi the diagnoses, the doctor's initial impressi of the illness, and their final grading. The init impression was that 86% of the babies were w or mildly ill and 14% moderately ill, where at the end of the assessment (after they h examined the baby and seen the Baby Che score and its interpretation) the babies we considered to be sicker, 76% were considered be well or mildly ill (grade 4), 19% suitable to managed at home with careful observation by capable mother, and 6% to require hospi admission (grades 1 and 2).

Baby Check has also been designed for use parents at home, where 97% of babies sco less than 8.[6] In this study scores less than occurred in 64% of babies. Baby Check advis parents that a baby with a score in this range unlikely to need medical attention (see table This study has also shown that babies wi scores in this range seen by GPs were either w or had only minor illnesses, mainly upp respiratory infections or viral infections. T general practitioners considered that 89% them were well or mildly ill although 25% we given prescriptions for thrush, conjunctiviti otitis media, bronchitis, and upper respiratory tract infection.

If the mothers with low scoring babies had had access to Baby Check's advice and initially sought help from their health visitor or midwife rather than their GP, most of the babies would have been treated adequately and only a few referred to the doctor. This suggests that the widespread use of Baby Check by mothers in the community could reduce the numbers of babies taken to the GP with minor problems. In their comments several GPs said they also found the score card useful to reassure mothers that their babies were not seriously ill.

Intermediate scores—that is, 8 to 19—were obtained for 31% of the babies. With a score in this range a baby may be either mildly, moderately, or seriously ill. This might be considered unhelpful because it does not give firm guidelines about decision making. However, an intermediate score alerts the GP and parents to ensure the baby is carefully observed and reassessed. The scoring system can be repeated to determine whether the score is rising or falling, and this can be used to indicate whether the baby's condition is deteriorating or improving.

This study confirms that high scores of 20 or more are uncommon and should be taken seriously. The babies assessed in this study were probably some of the illest babies seen by GPs and yet only 5% scored 20 or more. In the field trials where babies were scored by mothers at home only 0·1% of the scores done routinely were over 20.[6] Of the four babies with high scores in this study, two with scores of 29 and 33 were admitted to hospital very ill with bronchiolitis and congenital adrenal hyperplasia, and the other two, although not admitted, had a number of worrying symptoms and signs and needed to be carefully observed at home. In the field trial of babies being scored in hospital over 90% of the babies with a score of 20 or more were considered to need admitting to hospital.[7]

The scoring system is designed to aid the assessment of acute systemic illness in babies. Clearly it would not be needed in babies with an obvious problem, such as injury, a convulsion, or failure to thrive, nor can it take account of the child's history or family circumstances. There may also be conditions that are not serious, such as thrush or conjunctivitis which still need treatment. It is designed to be used in the difficult assessment of babies with non-specific illnesses. Some doctors are inexperienced in assessing such babies. The use of Baby Check by GPs would help them to assess babies thoroughly and quantify the severity of the illness objectively.

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Copies of the Baby Check score card and booklet can be obtained from the authors.

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Archives of Disease in Childhood 1991; 66: 115–120

Field trials of the Baby Check score card in hospital

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Abstract
The Baby Check score card was used by junior paediatric doctors to assess 262 babies under 6 months old presenting to hospital. The duty registrar and two consultants independently graded the severity of each baby's illness without knowledge of the Baby Check score. The registrars assessed the babies at presentation while the consultants reviewed the notes. The consultants and registrars agreed about the need for hospital admission only about 75% of the time. The score's sensitivity and predictive values were similar to those of the registrars' grading. The score's specificity was 87%. Babies with serious diagnoses scored high, while minor illnesses scored low. The predictive value for requiring hospital admission increased with the score, rising to 100% for scores of 20 or more. The appropriate use of Baby Check should improve the detection of serious illness. It could also reduce the number of babies admitted with minor illness, without putting them at increased risk.

Baby Check is a score card developed to help parents and health professionals assess the severity of acute illness in babies under 6 months old.[1 2] It consists of 19 checks (seven questions about symptoms in the previous 24 hours and 12 simple examination signs), each carrying a score. The scores for positive checks are added together. The higher the total score, the sicker the baby.

Two versions have been produced: an illustrated booklet for parents and a card for doctors, health visitors, and midwives.[1 3] The card includes definitions, a table showing the chance of the baby being well or mildly ill, moderately ill, or seriously ill at different scores, and notes about low scoring conditions which require attention.

For parents, the total score is divided into four groups, a score between 0 and 7 means the baby is well or only mildly ill and is unlikely to need medical attention at present, a score between 8 and 12 that the baby is unwell but is not seriously ill, and that advice should be sought from a doctor, health visitor, or midwife, a score between 13 and 19 that the baby is ill and needs to be seen by a doctor, and a score of 20 or more that there is a high chance of serious illness, and the baby needs to be seen by a doctor straight away. These cut offs were identified using Receiver Operating Characteristic curves and predictive values.

The score card simulates the clinical judgment of the original assessor, an experienced paediatrician, accurately. However, the predictive values, sensitivity, and specificity of the score apply only to the original study population. Before Baby Check can be adopted, it must be shown to be accurate in identifying seriously ill babies in other populations. This paper reports a field trial in which Baby Check was used to score babies presenting to hospital with an acute illness.

Methods

During 44 weeks, 13 paediatric house officers at Addenbrooke's Hospital were asked to score every baby under 26 weeks old presenting for assessment of an acute illness. They received no instruction in the use of the score card. As soon after presentation as possible, without knowledge of the score, the duty paediatric registrar graded each baby's illness on a seven point scale, ranging from: 'Baby needs urgent hospital treatment for a life threatening condition' to: 'Well baby not requiring any special care or treatment'. The registrars' grading reflected the baby's state at the time of presentation. Two consultant paediatricians reviewed each baby's notes after discharge, using the same scale and without knowledge of the score. Their gradings took into account the investigation results, diagnosis, treatment, and outcome. For the analyses, these gradings were simplified into four categories, shown in table 1.

Baby Check's performance in identifying the babies the consultants considered needed admitting for observation or treatment was compared with that of the registrars' grading. Differences in sensitivity, specificity, and predictive accuracy between the score and the registrar's grading were explored using χ^2 analyses.

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Table 1 Registrars' and consultants' gradings of illness severity. Results are number (%) of gradings

Grade of illness severity	*Registrars (n=196)*	*Consultant A (n=259)*	*Consultant B (n=260)*
(1) Has a serious illness needing hospital treatment	45 (23)	113 (44)	74 (28)
(2) Requires hospital admission for observation due to uncertainty about the severity of the illness	74 (38)	65 (25)	86 (33)
(3) Needs careful observation and treatment. Could be managed at home by a capable mother	47 (24)	59 (23)	65 (25)
(4) Mildly ill or well. Could be managed at home by any mother	30 (15)	22 (8)	35 (14)

Results

During the study 303/357 (85%) babies presenting to casualty were seen by the paediatric team and were thus eligible. The house officers scored 243 (80%). Nineteen babies presenting to the wards were also scored. Of these 262, 196 (75%) had their illnesses graded by the registrars: 172 (88%) were seen shortly after presentation, and in the remainder the registrar graded the illness from the notes a few hours later, using only the information available at the time of presentation. Fourteen babies who were sent home and 52 who were admitted did not have their illness graded by the registrar. Two hundred and fifty nine (99%) babies had their illness graded by consultant A and 260 (99%) by consultant B.

SEVERITY OF THE BABIES' ILLNESSES

Of the babies scored, 227 (87%) were admitted (seven to intensive care) and 34 (13%) sent home (one not recorded). The median stay was two days, ranging from a few hours to 99 days; none died.

The babies had a broad range of diagnoses, from minor complaints such as nappy rash to serious illnesses such as meningitis.

Table 1 shows the registrars' and consultants' gradings of illness severity.

PROFILE OF SCORES

The scores ranged from 0 to 57 (fig 1), with a median of 12 (10th and 90th centiles 0, 34). The median score for babies sent home was 3 (0, 7),

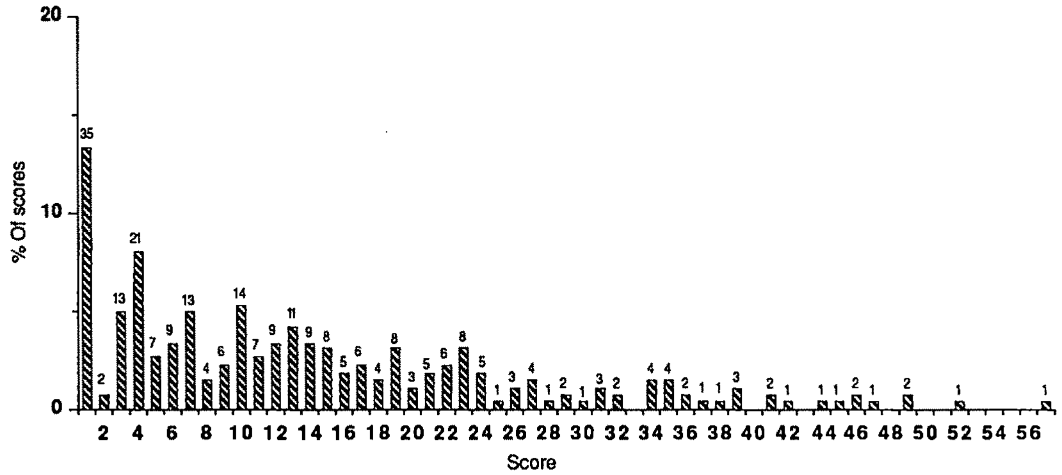

Figure 1 Profile of scores (n=262). The numbers of babies with each score are shown at the top of each column.

Table 2 Diagnoses and gradings of illness severity in a random selection of babies in each score group

Diagnosis	*Score*	*Illness gradings*		
		Registrars	*Consultant A*	*Consultant B*
Scores of 0 to 7				
Nasal obstruction	0	3	3	3
Vomiting—no cause found	0	4	3	3
Pyloric stenosis	0	3	1	1
Minor head injury	0	4	4	3
Asymptomatic heart murmur	0	4	4	4
Vomiting—no cause found	4	3	3	4
Well, crying baby	4	—	4	4
Drowsy—no cause found	5	2	2	2
Upper respiratory tract infection	7	3	3	3
Scores of 8 to 12				
Acute otitis media	8	—	2	2
Upper respiratory tract infection	9	4	3	3
Bronchiolitis	10	3	1	3
Viral infection	10	3	1	2
Pyloric stenosis	10	1	1	2
Anal fissure	11	—	2	3
Staphylococcal skin infection	12	1	1	1
Bronchiolitis	12	2	2	2
Scores of 13 to 19				
Viral infection	13	3	3	[illegible]
Gastroenteritis	14	3	3	[illegible]
Bronchiolitis	14	—	1	[illegible]
Septicaemia	15	2	1	[illegible]
Bronchiolitis	15	3	1	2
Upper respiratory tract infection	15	3	4	3
Viral infection	16	2	3	2
Convulsion	18	—	1	2
Bronchiolitis	19	2	1	3
Renal dysplasia	19	2	1	1
Scores of 20 or more				
Bronchiolitis	24	2	2	1
Bronchiolitis	27	3	2	[illegible]
Bronchiolitis	27	1	1	[illegible]
Urinary tract infection	29	2	1	[illegible]
Viral pneumonia	31	2	1	[illegible]
Vomiting—no cause found	34	—	3	[illegible]
Intussuception	34	1	1	[illegible]
Near miss cot death	37	1	1	[illegible]
Bacterial pneumonia	52	1	1	[illegible]
Irreducible inguinal hernia	49	1	1	[illegible]

and for those admitted to paediatric wards and to intensive care, 13 (3, 34) and 30 respectively. Those graded by the registrars as needing hospital treatment (grade 1) had a median score of 27 (10, 46). Those graded as well or mildly ill (grade 4) had a median score of 4 (0, 16).

The score groups

Of the 262 scores, 100 (38%) were between 0 and 7, 40 (15%) 8 to 12, 51 (20%) 13 to 19, and 71 (27%) 20 or more.

Table 2 shows the diagnoses and gradings of illness severity for a random selection of babies in each score group.

SCORES FOR DIFFERENT DIAGNOSES

Table 3 shows the distribution of scores for some well defined diagnoses. The highest scores (52, 57) were for babies with bacterial pneumonia.

THE SCORE COMPARED WITH THE GRADINGS OF ILLNESS SEVERITY

A registrar and both consultants graded the illness in 193 (74%) cases. Table 4 shows comparisons of the gradings. Table 5 shows the score groups compared with the gradings. Data for 193 babies are presented to facilitate comparisons using the same cohort throughout. Using all the available data gave very similar results.

Concordance between the paediatricians

The three paediatricians' gradings were compared for concordance using the percentage agreement and the $\varkappa$,[4, 5] with a cut off between grades 2 and 3 (that is, whether or not the baby needed admitting to hospital). The results were: registrars compared with consultant A, 74% agreement, $\varkappa=0\cdot42$; registrars compared with consultant B, 81% agreement, $\varkappa=0\cdot60$; and consultant A compared with consultant B, 78% agreement, $\varkappa=0\cdot50$.

Table 3 Scores for different dianoses

Diagnosis	*No of babies*	*Median*	*Range*
Bacterial pneumonia	2	54	52–57
Meningitis	3	35	22–42
Intussusception	4	31	30–45
Urinary tract infection	3	29	11–36
Inguinal hernia	8	23	13–49
Bronchiolitis	48	22	7–49
Pyloric stenosis	9	13	0–39
Gastroenteritis	20	13	2–26
Convulsion	5	12	0–18
Abscess/cyst	8	10	0–44
Upper respiratory tract infection	36	7	0–31
Apnoea	14	5	0–46
Constipation	4	4	3–7
Well/teething	14	4	0–15

Table 4 Comparison of the registrars' and consultants' gradings (1–4) of illness severity (n=193)

		Consultant A illness grading			
		4	3	2	1
Registrars' illness grading	4	8	12	3	6
	3	2	18	12	14
	2	2	12	23	37
	1	—	1	6	37
		Consultant B illness grading			
		4	3	2	1
Registrars' illness grading	4	9	16	4	—
	3	6	22	15	3
	2	2	11	31	30
	1	—	1	13	30
		Consultant A illness grading			
		4	3	2	1
Consultant B illness grading	4	4	10	1	2
	3	7	19	15	9
	2	1	12	22	28
	1	—	2	6	55

Table 5 Score groups compared with registrars' and consultants' gradings of illness severity (n=193)

	Registrars' illness grading			
Score group:	4	3	2	1
0 to 7	23	23	19	3
8 to 12	3	5	16	5
13 to 19	3	15	16	6
20 or more	—	3	23	30
	Consultant A illness grading			
Score group:	4	3	2	1
0 to 7	11	22	17	18
8 to 12	—	8	7	14
13 to 19	1	10	10	19
20 or more	—	3	10	43
	Consultant B illness grading			
Score group:	4	3	2	1
0 to 7	14	30	20	4
8 to 12	2	8	11	8
13 to 19	1	11	15	13
20 or more	—	1	17	38

Concordance between the score and the paediatricians

The same procedure was used to compare the score and the illness gradings, using the same cut off between grades 2 and 3, and a score of 13 or more. The results were: score compared with registrars, 67%, $\varkappa=0\cdot34$; score compared with consultant A, 64%, $\varkappa=0\cdot28$; and score compared with consultant B, 71%, $\varkappa=0\cdot42$.

Thus the agreement between the score and the paediatricians was slightly less good than among the paediatricians.

SENSITIVITY

Babies requiring hospital treatment (grade 1)

There was no significant difference between the sensitivity of the score and that of the registrar in identifying babies the consultants graded as needing hospital treatment. The sensitivity of the registrars was 37/94 (39%) for consultant A and 30/63 (48%) for consultant B. The sensitivity of a score of 20 or more was 43/94 (46%) and 38/63 (60%) respectively.

Babies requiring hospital admission (grades 1 and 2)

A score of 13 or more identified significantly fewer of the babies graded by the consultants as requiring admission than the registrar did ($p<0\cdot05$). The sensitivity of the registrars was 103/138 (75%) for consultant A and 104/126 (83%) for consultant B. The sensitivity of a score of 13 or more was 82/138 (59%) and 83/126 (66%) respectively.

SPECIFICITY

The specificity of the registrars identifying babies the consultants graded as mildly ill (grade 4) was 8/12 (67%) and 9/17 (53%) respectively. The specificity of a score of 0 to 7 was 11/12 (92%) for consultant A and 14/17 (82%) for consultant B.

A low score thus had a higher specificity than the registrars' grading. The difference was not significant due to the small numbers.

PREDICTIVE VALUES

Individual scores

Figure 2 shows the predictive values of each score for each grade of illness, averaged over the two consultants (n=259). The higher the score the sicker the baby. The chance of needing hospital admission or treatment increased with the score. For example, the predictive value for needing hospital treatment was low at low scores, rising to 67% at a score of 20 and 100% at a score of 28.

Few babies scoring over 8 were graded as mildly ill. The number graded as needing careful observation at home (grade 3) also decreased as the score increased.

Score groups

Babies requiring hospital treatment (grade 1): scores of 20 or more—A score of 20 or more was as predictive as the registrars' grading in identifying babies needing hospital treatment. The registrars' grading had predictive values of 37/44 (84%) for consultant A and 30/44 (68%) for consultant B (table 4). The predictive values of a score of 20 or more were 43/56 (77%) and 38/56 (68%) respectively (table 5).

Babies requiring hospital admission (grades 1 and 2): scores of 13 or more—The predictive values of the registrars' grading were 103/118 (87%) for consultant A and 104/118 (88%) for consultant B. The predictive value of a score of 13 or more for being graded as needing admission was 82/96 (85%) for consultant A and 83/96 (86%) for consultant B. These results were not significantly different.

Babies graded as well or mildly ill (grade 4): scores of 0 to 7—The registrars' grading a baby as being mildly ill or well had a predictive value for being graded the same of 8/29 (28%) for consultant A and 9/29 (31%) for consultant B (table 4). The predictive values of a score between 0 and 7 were 11/68 (16%) and 14/68 (21%) respectively (table 5). These results were not significantly different.

FALSE NEGATIVES AND FALSE POSITIVES

These were identified using the registrars' grading, because this was recorded at the same stage of the illness as the score. Misclassifications arising from the consultants' gradings were very similar.

False negatives: babies with low scores requiring hospital treatment (grade 1)

Three babies (7%) graded 1 had scores between 0 and 7. Their diagnoses were apnoeic episode, hydrocephalus, and pyloric stenosis (only scored for vomiting). Five (11%) scored 8 to 12. Their diagnoses were thyroglossal cyst, proctitis, viral infection (initially thought to be meningitis), pyloric stenosis, and staphylococcal skin and eye infection.

False negatives: babies with low scores requiring hospital observation (grade 2)

Nineteen babies (16%) graded 2 scored between 0 and 7. The diagnoses made were: apnoeic episodes (n=5), upper respiratory tract infection

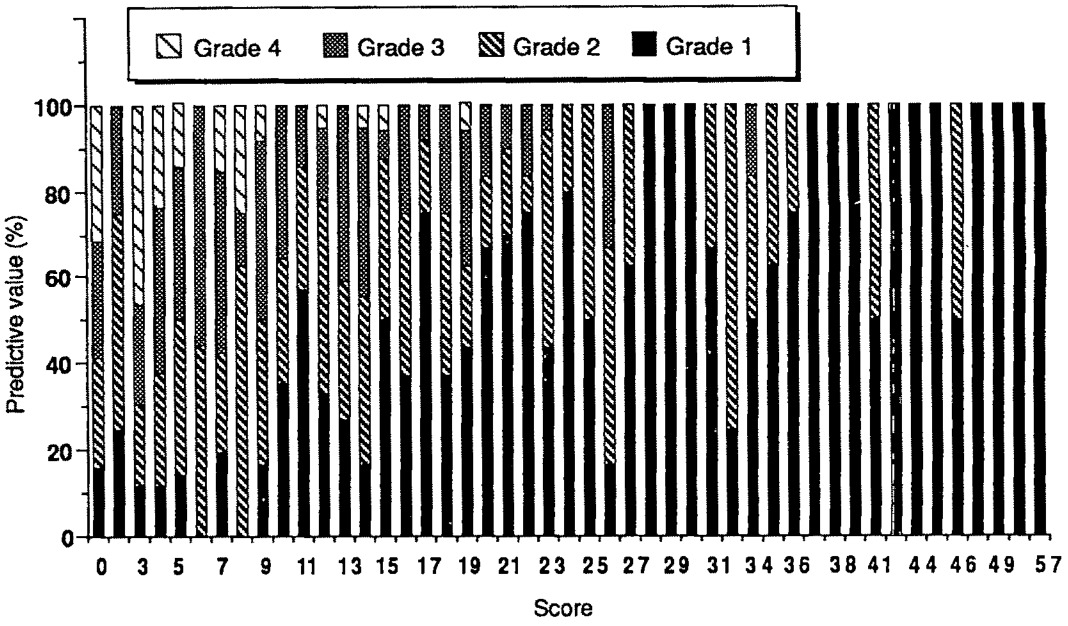

Figure 2 Predictive value of each score for each grade of illness (n=259). Three babies did not have their illness graded by both paediatricians; they scored 16, 34 and 39. The four grades of illness are defined as: Grade 1, has a serious illness needing hospital treatment. Grade 2, requires hospital admission for observation due to uncertainty about the severity of the illness. Grade 3, needs careful observation and treatment. Could be managed at home by a capable mother. Grade 4, mildly ill or well. Could be managed at home by any mother.

(n=3), bronchiolitis (n=2), gastro-oesophageal reflux (n=2), and one case each of convulsion, non-accidental injury, infected umbilicus, vomiting (no cause found), gastroenteritis, drowsiness (no cause found), and viral infection.

False positives: babies with high scores graded as well or mildly ill (grade 4)

Three babies (10%) graded 4 had scores of 13 or more. None scored over 19. The diagnoses made were: proctitis, upper respiratory tract infection, and jaundice.

Discussion

These results show that Baby Check provides an accurate means of grading the severity of acute systemic illness in babies. The predictive value for serious illness increases with the score. Babies with serious diagnoses score high and those with minor illnesses score low. The score has a high specificity. The sensitivity and predictive value are similar to a paediatric registrar's grading of illness severity.

There is no gold standard to measure illness severity, and the field trial shows how difficult it is, even for experienced paediatricians. They only agreed about whether a baby needed admitting three quarters of the time. Many of the babies had non-specific illnesses which were difficult to assess, and about two thirds of admissions were because of uncertainty about the severity of the illness. The agreement between the score and the paediatricians was only slightly less good than that between the paediatricians themselves.

In a study of babies presenting to hospital it might seem strange that over half scored less than 13. But many of the babies were not seriously ill. About 40% were graded as suitable for home management, provided the mother could cope. The number admitted reflects hospital policy—babies presenting for acute assessment are admitted for observation unless they are obviously well.

Although the use of 'cut offs' is necessary to explore the score's sensitivity and specificity, they are a crude test of its accuracy. The score provides a continuous measure of illness severity. The risk of serious illness increases with the score (fig 2). The irregularities in the predictive values are due partly to the small numbers of babies at the higher scores. The predictive values from the original population shown on the professionals' version of Baby Check are smoothed.[1]

The common diagnoses gave rise to a range of scores and paediatricians' gradings, reflecting the variation in the severity of disease. Baby Check is thus useful in grading illness severity in variable conditions such as bronchiolitis. Serious conditions such as meningitis and pneumonia always scored 20 or more. Diagnoses such as jaundice and convulsions were associated with lower scores, reflecting the fact that they often have few systemic signs.

Scores of 20 or more had a predictive value for being graded as needing admission of over 95%, with over 70% graded as needing hospital treatment. Scores in this range were as effective as the registrars in identifying the sickest babies—those graded as requiring treatment for a known serious condition. Most babies with scores over 19 had serious diagnoses.

A score of 13 or more was slightly less sensitive than the registrars in identifying babies graded as needing admission (grades 1 and 2), identifying approximately two thirds, with a positive predictive value of around 85%.

Baby Check must not miss seriously ill babies. The low scoring babies graded as needing admission fell into two groups: some had specific conditions such as convulsions, abscesses, and injuries that have few systemic signs but still need investigation. The score card is not designed to assess such conditions, which are easily recognisable. It includes a warning that they may give a low score but still warrant careful assessment. The second group comprised those admitted because of uncertainty about how the illness might progress. These babies had a wide range of illnesses and scores. These two factors also accounted for the poor negative predictive value of the lower scores.

One fifth of the babies graded by the registrars as needing hospital treatment (grade 1) scored less than 13. According to the consultants, however, the registrars overestimated the number needing treatment in a quarter of babies.

The specificity of the score was higher than that of the registrars. Some 87% of the well or mildly ill babies scored less than 8.

The false positive rate was low. Only three babies graded by the registrars as mildly ill scored over 12. None scored over 19. All were graded more seriously by the consultants.

Predictive values and sensitivities apply only to the population from which they were derived. In this trial Baby Check was tested by multiple observers in an environment that differed from the original one. The predictive values from the original population, shown on Baby Check,[1] and the values observed in this study differ mainly at the lower scores. The original study included a large community cohort,[1 2] so that most of the low scoring babies were well.

Baby Check is designed for use by parents at home, general practitioners, health visitors, and midwives in the community and junior doctors in hospital. In each of these environments the prevalence of illness is different, which will affect the interpretation of the lower scores. At home most babies are well and achieve low scores.[3] A baby with a low score at home has more than a 90% chance of being well or mildly ill.[1 2] In hospital many low scoring babies have conditions (such as a convulsion) which obviously need attention, as demonstrated by the poor predictive value of the low scores in this study.

Although many of the babies scoring 13 to 19 were graded as requiring admission once they had presented to hospital, few were thought to need treatment for a known serious illness, and if seen by a general practitioner some of these babies might have been managed at home with careful review. Scores of 20 or more are rare in the community,[1–3 5] however, and this study confirms that babies who achieve them warrant urgent assessment wherever they are seen.

The score provides an objective means of grading a baby's illness, which can be used in association with clinical judgment to decide what action should be taken. It should help doctors assess the severity of acute systemic illness in babies. The score is of particular value in identifying the well and the most seriously ill babies, and should assist in the management of the large group of babies who are currently admitted because of uncertainty about the severity of the illness. Provided the home circumstances and previous history were satisfactory, some of those with low scores could be sent home and kept under review by the mother and the general practitioner using Baby Check,[3 6] returning to hospital if the score increased.

The appropriate use of Baby Check in hospital and in the community should improve the detection of serious illness. It could also reduce the number of babies admitted with mild illness, without putting them at increased risk.

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Copies of the Baby Check score card and booklet can be obtained from the authors.

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Endoscopic retrograde cholangiopancreatography in infantile cholestasis

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Abstract

The difficulty of distinguishing surgically correctable causes of conjugated hyperbilirubinaemia in infants from other causes means that some infants may undergo laparotomy and intraoperative cholangiography unnecessarily, and others may be referred for surgery too late. In an attempt to improve the diagnostic accuracy in infants with conjugated hyperbilirubinaemia when standard methods produced equivocal results, we have been using prototype paediatric duodenoscopes (PJF 7·5 and XPJF 8·0; Olympus) to perform endoscopic retrograde cholangiopancreatography (ERCP). From 159 infants with conjugated hyperbilirubinaemia, 11 were referred for ERCP, which was performed in nine. In four in whom bile ducts were definitely visualised laparotomy was avoided. Operative cholangiography confirmed patent bile ducts in one in whom visualisation had been uncertain. Three of four in whom bile ducts were not seen had extrahepatic biliary atresia. Visible bile drainage in the fourth excluded atresia. No major complications ensued but there was radiological evidence of gall bladder perforation in one (common hepatic duct block) and overinflation with air was a problem until finer cannulae (Wilson-Cook) were introduced. In appropriately selected patients with conjugated hyperbilirubinaemia, ERCP with paediatric duodenoscopes in experienced hands may provide useful diagnostic information.

Conjugated hyperbilirubinaemia in infants may be due to intrahepatic disease or, less commonly, disorders of the extrahepatic bile ducts. It may occur in association with a wide range of metabolic, endocrine, infectious, or familial disorders. Particular difficulty may occur in distinguishing three relatively common disorders: idiopathic neonatal hepatitis, arteriohepatic dysplasia, and extrahepatic biliary atresia (EHBA). The first two conditions have a good prognosis with medical management, but the last requires urgent surgical treatment. Hepatoportoenterostomy by a skilled surgeon performed before 8 weeks of age produces a normal plasma bilirubin concentration in approximately 85% of infants, but with later surgery this is achieved in only one third.[1] Eighty seven per cent of the children who have cleared the jaundice after surgery are alive with a good quality of life 15 years later.[2] Without successful bile drainage these infants die of cirrhosis, usually by 2 years of age,[3] unless liver transplantation is available. Such patients constitute the major paediatric indication for liver transplantation.

To date, a prelaparotomy diagnosis of EHBA is made by demonstrating complete cholestasis and by systematically excluding other disorders, particularly endocrine or genetic diseases such as α_1 antitrypsin deficiency or cystic fibrosis, which may give appearances on a liver biopsy specimen suggestive of EHBA. Even if assessed by a histologist skilled in liver pathology of infancy there remains 10–15% of the cases in which either the changes in the specimen are equivocal or associated features such as congenital heart disease (for example, peripheral pulmonary stenosis) cause diagnostic uncertainty. In our experience, a correct diagnosis is obtainable in about 90% of the cases.[4] For the remainder, laparotomy with intraoperative cholangiography should confirm or exclude EHBA, but in practice even an experienced surgeon may remove small but patent ducts in infants with severe cholestasis due to intrahepatic disease. To avoid unnecessary laparotomy, since November 1987 we have attempted to demonstrate patency of the extrahepatic bile ducts by endoscopic retrograde cholangiopancreatography (ERCP), using prototype neonatal duodenoscopes, in cases of conjugated hyperbilirubinaemia and complete cholestasis in whom the diagnosis was uncertain.

Patients and methods

Over the period November 1987 to January 1990, 159 infants with conjugated hyperbilirubinaemia were admitted for diagnosis and management to the paediatric liver service of King's College Hospital.

Investigations included standard haematological and liver function tests, ultrasound examination of the liver and biliary system, screening for viral and bacterial infections, α_1 antitrypsin phenotype, sweat test, methyl bromoiminodiacetic acid (methyl bromida) scan, liver biopsy, and bone marrow examination. In 104 infants the jaundice was considered due to intrahepatic disease and proved to be so on follow up. Forty four were considered to merit laparotomy and this decision was correct in all cases. In 11 infants with complete cholestasis (acholic stools, no excretion on methyl bromida scan) the clinical and pathological features were equivocal, the liver histology showing mixed hepatitic and biliary features, the latter falling short of a clear picture of biliary atresia. ERCP was performed in nine of these infants (six boys) at a median age of 13 weeks (range 7–42) and at a median weight 4·45 kg (range 3·7–6·2). For

Clinical details and ERCP findings of the nine children investigated

Sex	*Age (weeks)*	*Weight (kg)*	*ERCP findings (filling of pancreatic duct/common bile duct)*	*Final diagnosis*
F	20	5·6	Pancreatic duct only	EHBA
M	8	4·3	Pancreatic duct only	EHBA
F	11	4·5	Pancreatic duct only	EHBA
M	42	6·2	Both (common hepatic duct block)	?
M	13	3·7	Both (hypoplastic biliary tree)	Arteriohepatic dysplasia
M	19	4·5	Both (hypoplastic biliary tree)	Arteriohepatic dysplasia
F	22	4·4	Pancreatic duct only (free bile drainage)	?
M	9	3·9	Both (normal)	Idiopathic neonatal hepatitis
M	7	3·7	Pancreatic duct only ? (equivocal filling)	Idiopathic neonatal hepatitis

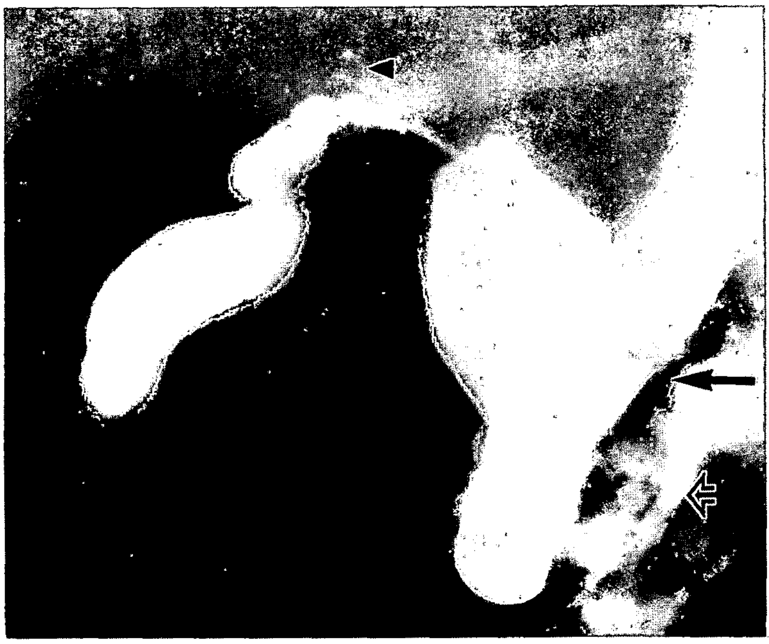
ERCP=Endoscopic retrograde cholangiopancreatography.
EHBA=extrahepatic biliary atresia.

the other two infants either the operator (MLW) or the endoscope were unavailable.

The endoscopes used were specially designed Olympus OES duodenoscopes PJF 7·5 (in six patients) and XPJF 8·0 (in three patients) of 7·5 and 8·0 mm external diameter respectively. The biopsy channel of each of these endoscopes was of 2 mm calibre but the PJF 7·5 lacked a bridge/elevator mechanism. Cannulae were of the tapered tip type. In one case cannulation could only be achieved by the use of a fine 'pre-cut' knife as a steerable cannula (Olympus). In the last patient a 3FG cannula was employed (Wilson-Cook). Non-ionic radiography contrast medium (Niopam 300) was used. The procedure was performed by a single endoscopist under general anaesthesia in eight infants and under sedation in one. Patients were intubated while in the supine position, sometimes with the help of a laryngoscope, and ERCP was thereafter performed in the standard manner. However, the narrow confines of the duodenum in infants compound the difficulties of the procedure. With the PJF 7·5, 'blind' cannulation was sometimes necessary due to the lack of a 'bridge' mechanism.

Results

Successful cannulation of the papilla was obtained in all nine infants (table). In three, only the pancreatic duct was demonstrated. In all of them EHBA was diagnosed at subsequent laparotomy and confirmed by histological examination of the excised tissue. Operative cholangiogram was not performed.



Endoscopic retrograde cholangiopancreatogram on a 19 week boy with conjugated hyperbilirubinaemia. Minute intrahepatic ducts (arrow head) and common bile duct (solid arrow), normal gall bladder, and pancreatic duct (hollow arrow) are shown. Eventual diagnosis was arteriohepatic dysplasia.

In one child there was simultaneous filling of the pancreatic duct and common bile duct, but no filling of the intrahepatic bile ducts and a common hepatic duct block was suspected. As the child had severe biliary type fibrosis and was already 42 weeks' old, it was decided not to proceed to a laparotomy in view of the possibility of a future liver transplant. The child was discharged with no definitive diagnosis. He was alive, having bled from oesophageal varices, at the age of 2·6 years and liver function tests showed features of compensated cirrhosis with a serum bilirubin concentration of 206 μmmol/l, having been 230 μmo/l at the time of ERCP.

In one further infant pancreatic cannulation only was achieved, but bile was seen to be draining freely from the papilla before cannulation, and EHBA was thus excluded. The interval between the methyl bromida scan showing no secretion and the ERCP was 14 days. The jaundice subsequently cleared completely and, at the age of 1 year, hepatosplenomegaly persists but liver function tests are only mildly abnormal.

One child with severe giant cell hepatitis and moderate bile duct proliferation had a normal biliary tree at ERCP at 9 weeks of age. He progressed to chronic liver disease and died of liver failure at the age of 6 months. No aetiological factor was identified. His parents denied permission for a postmortem examination.

In one infant, aged 7 weeks, the liver biopsy specimen showed giant cell transformation with bile duct reduplication and mild portal tract oedema. ERCP showed a normal pancreatic duct, but no biliary filling could be seen on screening. After removal of the endoscope, a ductular structure in the region of the common bile duct and common hepatic duct, which had been hidden by the endoscope during the procedure, was seen. In view of the poor definition of the films, however, no firm conclusion could be made. The child underwent exploratory laparotomy with intraoperative cholangiogram, which showed patent intrahepatic and extrahepatic bile ducts. The child is improving and a provisional diagnosis of idiopathic neonatal hepatitis has been made.

Two infants had heart murmurs compatible with peripheral pulmonary artery stenosis and posterior embryotoxon (in one in association with butterfly vertebrae). Their liver biopsy specimens, though, showed cholangitic portal tract changes including oedema and bile duct proliferation. In one of them ERCP showed a normal pancreatic duct, cystic duct and gall bladder, but narrow common bile duct (maximum diameter of 0·48 mm) and main hepatic duct branches (<0·36 mm) (figure). The films of the other patient were of poor quality because of spillage of contrast and inadequate injection, but they showed a normal calibre common bile duct and cystic duct, while the common hepatic duct was narrow, measuring only 0·3 mm in diameter. No intrahepatic ducts were seen, possibly due to poor filling. In both cases, a diagnosis of arteriohepatic dysplasia was made, supported by the subsequent development of hypercholesterolaemia and the typical facial appearance. At follow up both are well but with moderate to severe failure to thrive and abnormal liver function tests at the age of 31 and 32 months.

ERCP was carried out without serious complications in all nine cases. Despite minimal use of the air insufflator, however, abdominal distension was noted in all but the last patient, often making chest inflation by the anaesthetist difficult. The problem was due to the cannula completely filling the biopsy channel, thus preventing the use of the aspiration mechanism. Recently the use of finer cannulae, 3FG and 4FG (Wilson-Cook), has reduced this problem. In the patient with no duct filling beyond the common hepatic duct a small perforation of the gall bladder was seen radiologically but there were no clinical sequelae.

All infants recovered without problems from anaesthesia and were able to resume feeding the same day.

Discussion

Portoenterostomy is a life saving operation in patients with EHBA, particularly if performed before the age of 8 weeks. All efforts should be made to diagnose this condition as soon as possible. Exploratory laparotomy performed to exclude it in dubious cases should be avoided, however, because of possible deterioration of liver disease due to surgery and because it may compromise future hepatic transplantation. In the present study ERCP was able to diagnose or exclude accurately EHBA in eight of nine cases who otherwise would have required laparotomy.

The procedure was safe, although further modifications to the equipment may improve success and safety. The problem of abdominal distension during the procedure, which has caused a gastric perforation in a previous series,[5] is reduced by the use of finer cannulae, which allow suction to take place during the procedure. ERCP was performed under general anaesthesia in most cases to avoid restlessness during the procedure. In only one child no definitive interpretation of the ERCP finding was possible, requiring further investigation by intraoperative cholangiogram.

Before 1987, ERCP was only occasionally described in neonates.[6 7] In 1987 Guelrud *et al* reported a prospective study on unselected infants with conjugated hyperbilirubinaemia.[8] Using a previous Olympus prototype they were successful in cannulating the biliary tree in 20 of 23 consecutive infants aged 2–21 weeks. They were able to diagnose bile duct obstruction in five with biliary atresia, normal biliary tree in 13 with neonatal hepatitis, and a choledochal cyst in one patient. In a further case with choledochal cyst ERCP did not visualise the common bile duct. In a study in 12 infants the following year, Heyman *et al*, also using a previous Olympus prototype, achieved cannulation only in four of 12 attempts.[5] The poor success rate in that series is difficult to explain, but the authors were unable to find the papilla in three children. They suggested that papillary hypoplasia might be a consequence of neonatal hepatitis, though in the present series both cases with this diagnosis had normal papillae. Our results and those of Guelrud *et al* show that in infants it is usually impossible to cannulate the biliary and pancreatic ducts separately by appropriate manoeuvres of the cannula, unlike the situation in adults. In all four instances in our series and in 12 of 13 in that of Guelrud *et al* in which the bile duct was shown to be patent the pancreatic duct was also filled; no details of pancreatic opacification are given in the series of Heyman *et al*. On the other hand pancreatic duct visualisation and failure to opacify the biliary system in both our series and that of Guelrud *et al* was associated with a surgically correctable lesion of the biliary system in nine of 10 instances (EHBA in eight, choledochal cyst in one). In one of our infants, in whom the biliary system did not opacify at the same time as the pancreas, patency was assured as bile was seen to flow from the ampulla. In the two children with arterio hepatic dysplasia ERCP findings were distinctive, showing hypoplastic extrahepatic ducts and in one case very fine intrahepatic ducts.

There results suggest that if ERCP shows filling of the pancreatic duct without demonstration of the intrahepatic bile ducts laparotomy is essential. This must be performed by a surgeon with the skills and experience to diagnose and correct EHBA and other rarer biliary disorders and the confidence to leave hypoplastic but patent ducts in situ if the infant has intrahepatic disease. We conclude that ERCP using duodenoscopes designed for infants is a valuable addition to the management of selected children with conjugated hyperbilirubinaemia.

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Recurrent wheezy bronchitis and viral respiratory infections

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Abstract

Fifty four patients aged from 1 to 6 years who had had recurrent attacks of wheezy bronchitis were prospectively followed up for three months to find out if there was an association between different viral respiratory infections and episodes of wheezing. Of the 115 episodes of upper or lower respiratory tract symptoms, virus or *Mycoplasma pneumoniae* infections were diagnosed in 52 (45%). Thirty four of these (65%) were caused by coronaviruses or rhinoviruses. The patients had an average of 2·1 episodes of respiratory tract symptoms the total mean (SD) duration of which was 30 (2) days of the 92 days that followed. Wheezing occurred during 76 (66%) of the 115 episodes and during a third of these the patient was admitted to hospital because of severe dyspnoea. Wheezing started a mean (SD) of 43 (7) hours after the first symptoms of respiratory infection and persisted for 3·8 (4·2) days in patients in whom virus infection was diagnosed. The incidence of wheezing was not associated with IgE mediated atopy, with positive virological tests, or with fever during virus infection, but was associated with parental smoking and more than one sibling.

Wheezy bronchitis, also called asthmatic bronchitis, is an acute recurrent respiratory illness characterised by cough, rhonchi, and expiratory distress in young children with hyper-reactive airway disease.[1] Viral infections play a large part in exacerbations of wheezing attacks in these children,[2–4] but the mechanisms of virus induced airway obstruction are complex and only partially understood.[5–7] There is some epidemiological evidence that wheezy bronchitis represents a definite subdivision of wheezing disease.[8] Several authors, however, regard wheezy bronchitis and asthma as the same disorder, because these two diseases share common clinical signs and possible similarities in pathogenesis.[9–11]

Although the treatment of wheezy bronchitis usually follows the same regimen as bronchial asthma, some young patients do not seem to benefit from treatment with sympathomimetics.[12] Particularly controversial is the optimal treatment of a young child with recurrent wheezing who requires daily medication.[13]

This prospective study was conducted to obtain baseline information about the natural course of wheezy bronchitis and the role of different viral infections in children prone to recurrent attacks of wheezy bronchitis.

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Patients and methods

Children aged from 1 to 6 years who had attended the Department of Paediatrics, Turku University Hospital between September 1985 and August 1986 and who had had two or more attacks of wheezy bronchitis with one or more admission to hospital were invited to participate in the study. To ensure adequate cooperation in follow up, only children who lived within 50 km of the hospital were considered. These criteria were fulfilled by 62 children.

Fifty six of the children participated at the prestudy visit in September 1986. The parents were informed about the nature and requirements of the study and informed consent was obtained. A medical history was taken, and questions were asked about aspects of each child's environment. A physical examination was done, and a venous blood sample taken.

The parents of two patients did not contact us despite the fact that their children had repeated infections during the follow up period. These children were excluded and the study group therefore consisted of 54 children. The mean age of the patients was 3·2 years (range 1–6) and 40 of them (74%) were boys. Eighteen patients were being treated by daily inhalations (either beclomethasone or sodium cromoglycate), three of them were having additional theophylline, and three were taking theophylline alone.

The parents were asked to bring their child to the hospital emergency room within 48 hours if their child developed signs and symptoms of an acute respiratory infection, wheezing or dyspnoea during the three month follow up period from October to December 1986. During this visit a physical examination was made by one of us (JM) and a specimen of nasopharyngeal secretion was taken. Patients who wheezed were treated with oral or inhaled salbutamol, and those with more severe dyspnoea were treated in the emergency room with nebulised salbutamol. Patients with severe dyspnoea who failed to respond to the nebulised drug were admitted to hospital.

Parents recorded the symptoms of the child daily on a personal symptom card during the whole three month period. Two weeks after the examination that had taken place during the acute attack the patients were examined again, a venous blood sample for viral serology was taken, and the symptom card was checked. A new episode of respiratory infection or wheezing was considered to have occurred when the symptoms of the previous episode had disappeared at least seven days before the new one started.

In January 1987 all the children were evaluated again (post-study physical examination) and a venous blood sample was taken for viral serology.

The control group was taken from 112 sex and age matched controls selected from the official register of the general population in the Turku area; they had been asked to fill in a questionnaire about their medical history, environment, and development of respiratory symptoms during the year before the prospective study was carried out. Parents from 69 children (62%) responded. Fifty four of the controls (78%) were boys and the mean age of the group was 3·3 years. Control children were not followed up in the same way as the study group, but were included to compare the history of respiratory infections and wheezing in a random group of children of similar age.

RISK FACTORS

For retrospective analysis of the association between environmental factors and the predisposition of the children to wheeze, the study group and their controls were divided into groups according to the type of day care they received, exposure to cigarette smoke, and number of siblings. The symptoms of allergy, numbers of respiratory infections and courses of antibiotics during the preceding year were also recorded.

VIROLOGICAL STUDIES

Samples of nasopharyngeal mucus were collected by aspiration of secretions from the nasopharynx through the nostrils with a disposable mucus extractor (Vycon). For isolation of viruses a cotton stick was dipped into the samples of mucus and then placed into a phial containing 2 ml virus transport medium (0·5% bovine albumin in tryptose phosphate broth containing antibiotics). The phials were kept for less than two hours in iced water and transported to the laboratory, where they were stored at −70°C until assayed.

The specimens for isolation of viral antigens were kept at 4°C until studied. The mucus was diluted 1:5 in phosphate buffered saline containing 20% inactivated fetal bovine serum, 2% Tween 20, and merthiolate, and homogenised by sonication in a Branson sonifier cell disrupter (model B15; Branson Sonic Power Co). The specimens were tested simultaneously by enzyme immunoassay for adenovirus, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, influenza A and B viruses, and coronavirus OC43.[14–18]

Viral isolation was done as described earlier with some modifications.[19] Of each specimen, 100 µl were inoculated into duplicate roller tube cultures of HeLa 'Ohio' cells. The cultures were stored in a roller apparatus (12 rev/hour) at 33°C and examined microscopically every second day. After six days of incubation negative cultures were transferred to fresh medium and incubated for another week. On rare occasions this was done twice. Rhinoviruses were identified by their typical cytopathogenic effect and by lability to acid treatment.

Serum IgG antibodies to adenovirus, influenza A, parainfluenza 1, 2, and 3, coronaviruses OC43 and 229E, and IgG and IgM to *Mycoplasma pneumoniae* were measured by immunoassay techniques described earlier.[15 16 18 20]

ALLERGOLOGICAL STUDIES

Skin prick tests were done as recommended by the Northern Society for Allergology.[21] The allergens used were: birch, alder, grass, and mugwort pollen; alternaria and cladosporium moulds; cat and dog dander; and house dust mite (*Dermatophagoides pteronyssinus*) (Allergologisk Laboratorium, Copenhagen). Reactions of ⩾++ were considered positive. Skin prick tests could not be done on six children because of poor cooperation. Serum samples from these children were tested with radioallergosorbent tests (RAST) with the corresponding antigens. The tests were considered positive when class 2 or greater was obtained. Serum total IgE concentration was measured by Phadebas IgE PRIST (Pharmacia Diagnostics AB).[22]

STATISTICAL ANALYSIS

The results are shown as mean (SD) unless otherwise stated. The significance of differences between the study and the control groups were calculated by the χ^2 test when the distribution in the groups was normal, and otherwise by the Mann-Whitney U test. A probability of <0·05 was accepted as significant. In addition, stepwise logistic regression analysis was used to find the best explanatory power associated with wheezing symptoms during the follow up period, and expressed as odds ratios with 95% confidence intervals. Biomedical Computer Programs (BMDP) statistical software was used for the analyses.

Results

RETROSPECTIVE ANALYSIS

Of the 69 controls 15 (21%) had had wheezing attacks sometimes during their lives, six (9%)

Table 1 Medical histories of patients and control subjects during the year preceding the prospective study. Results are expressed as mean (SD)

Variable	*Patients (n=54)*	*Controls subjects (n=69)*	*p Value*
Episodes of common cold	7·9 (3·5)	2·6 (2·2)	<0·01
Otitis media	2·5 (4·4)	0·7 (1·2)	<0·01
Courses of antibiotics	4·0 (4·5)	1·1 (1·5)	<0·01
Wheezing episodes	9·5 (13·1)	0·2 (0·8)	<0·01
Admission to hospital for wheezing or dyspnoea	2·3 (0·3)	0	Not applicable

had had attacks of wheezing during the preceding 12 months, and four (6%) had visited the hospital outpatient department because of wheezing and dyspnoea. During the year preceding the prospective study, children in the study group had experienced significantly more respiratory infections than their controls (table 1). There were no significant differences, however, when type of day care, number of siblings, or exposure to cigarette smoke were compared (unpublished observations). Patients had had more symptoms suggestive of atopy (table 2).

ALLERGIES AMONG PATIENTS

Thirty one of the patients in the follow up group (57%) had serum total IgE antibodies more than two standard deviations above the mean of normal children in their age group. Skin prick tests (or RAST) were positive in half the children. Thirteen (24%) had positive reactions to dog dander, 12 (22%) to cat dander, three (6%) to dust mite, and one (2%) to *Cladosporium* sp. Positive reactions to some of the other antigens were found in 24 patients (44%).

To evaluate further the impact of IgE mediated atopy on the susceptibility of these children to respiratory infections and wheezing, a subgroup of highly atopic patients was compared with other children in the study group. The criteria of atopy were those suggested by Carlsen *et al.*[23] Patients who had both high IgE (2 SD above the mean or more) and positive reactions to skin prick tests (or RAST) were defined as highly atopic in this study. Twenty three patients (43%) fulfilled these criteria and were compared with the other 31 patients in the study group. Significant differences were found in histories suggestive of inhalation allergy (animals, pollen, or dust) or allergy in general (inhalation or food allergy, or both) but not in the incidence of wheezing attacks (table 3). There were no significant differences in the number of parents who smoked at home or the type of day care of these children.

Table 2 Incidence of symptoms suggestive of atopy in patients compared with control subjects. Results are expressed as number (%) of each group

Symptom	*Patients (n=54)*	*Control subjects (n=69)*	*p Value*
Atopic eczema	21 (39)	9 (13)	<0·01
Food allergy	26 (48)	14 (20)	<0·01
Reaction to cat or dog	25 (46)	4 (6)	<0·01
Reaction to pollen	18 (33)	6 (9)	<0·01
Reaction to house dust	16 (30)	3 (4)	<0·01

EPISODES OF RESPIRATORY ILLNESS

Fifty two (96%) of all patients had episodes of rhinorrhea or cough, or both, lasting 30 (2) days of the 92 days that followed. In total there were 115 episodes of respiratory symptoms (cough, rhinorrhea, wheezing, or dyspnoea), an average of 2·1 episodes/symptomatic child. Highly atopic children had less episodes than others; 1·7 (1·0) compared with 2·3 (1·1) (p<0·05).

In 74 episodes (64%), the patient was the first person in the family to develop symptoms of the common cold. This occurred significantly more often in children who were cared for in the day care centres (71%) or in other families (73%) than in those who were cared for at home (45%) (p<0·05).

A total of 46 patients (80%) had episodes of wheezing or dyspnoea during the follow up period. There was no difference in the number of wheezing episodes between highly atopic and other patients (mean 1·3 in both groups). Wheezing started 43 (7) hours (median 23) after the first respiratory symptoms and persisted for 5·0 (5·5) days. In only 11 of the 115 cases (10%) did the episode actually start with wheezing.

The duration of wheezing and dyspnoea was 9 (2) days (median 4) during the whole follow up period. To try and explain the occurrence of wheezing for 4 days or less, or longer than 4 days during the follow up period, stepwise regression was used to compare age, sex, medical histories, environmental factors, allergy, results of allergological tests, isolation of viruses, use of prophylactic theophylline or inhalation treatment, and bacterial complications during the episodes. The only explanatory variables found were smoking at home and having more than one sibling (odds ratios 4·8 and 3·0 with 95% confidence intervals 1·9 to 12·6 and 1·0 to 8·6, respectively).

During 25 (33%) of the 76 wheezing episodes

Table 3 Comparison of highly atopic patients (positive skin prick test and IgE concentration more than two standard deviations above the upper limit of the reference range) and other children prone to wheezing. Results are expressed as mean (SD) unless otherwise stated

Variable	*Highly atopic patients (n=23)*	*Other patients (n=31)*	*p Value*
Age (years)	3·9 (1·4)	2·8 (1·1)	<0·005
During life time:			
No (%) with symptoms suggestive of allergy	22 (96)	15 (48)	<0·001
No (%) with symptoms of inhalation allergy	20 (87)	12 (38)	<0·001
Wheezing attacks	22·1 (32·8)	12·8 (17·9)	0·2
Treatment with intravenous steroids and theophylline	1·0 (2·1)	0·7 (1·3)	0·5
Admission to intensive care unit	0	5 (16)	0·11*
During preceding 12 months:			
Wheezing attacks	9·6 (9·6)	9·5 (15·3)	0·9
Admissions to hospital for dyspnoea	2·8 (2·3)	2·0 (1·6)	0·04
Episodes of common cold	7·4 (3·3)	8·3 (3·7)	0·4
Courses of antibiotics	3·1 (2·7)	4·7 (5·5)	0·2
During follow up:			
Wheezing attacks	1·3 (0·8)	1·3 (1·1)	0·9
No (%) of admissions to hospital for dyspnoea	8 (35)	10 (32)	0·8
No (%) requiring intravenous treatment of dyspnoea	2 (9)	3 (10)	0·9
Episodes of common cold	1·7 (1·0)	2·3 (1·1)	<0·05
Diagnosed virus infections	1·0 (0·8)	0·9 (0·8)	0·7
No (%) requiring course(s) of antibiotics	5 (22)	13 (42)	0·1

*Fisher's exact test (two tailed).

Table 4 Incidence of respiratory infections, wheezing attacks, fever, and admissions to hospital in 54 children prone to wheezing who were followed up for three months

Laboratory findings	*No of respiratory infections*	*No (%) with wheezing attacks*	*No (%) with feverish episodes*	*No (%) requiring admission to hospital*
Positive:	52	30 (58)	20 (39)	6 (12)
Coronavirus	13	9 (69)	4 (31)	2 (15)
Rhinovirus	12	8 (67)	4 (33)	0
Adenovirus	5	1 (20)	2 (40)	1 (20)
Influenza A virus	4	1 (25)	4 (100)	1 (25)
Parainfluenza viruses 1–3	7	5 (71)	2 (29)	0
Mycoplasma pneumoniae	2	1 (50)	0	0
Dual infection	9	5 (56)	4 (44)	2 (22)
Negative	63	46 (73)	17 (27)	19 (30)
Total	115	76 (66)	37 (32)	25 (22)

Table 5 Comparison of episodes in which viruses were identified with those in which they were not

Variable	*Virus positively identified (n=52)*	*Virus not identified (n=63)*	*p Value*
Respiratory symptoms:			
Mean (SD) duration (days)	14·8 (9·1)	14·4 (9·8)	0·8
Fever:			
No (%) of episodes	20 (39)	17 (27)	0·2
Mean (SD) duration (days)	2·4 (1·5)	1·8 (1·1)	<0·05
Wheezing:			
No (%) of episodes	30 (58)	46 (73)	0·08
Mean (SD) duration (days)	3·8 (4·2)	5·8 (6·7)	0·08
Admissions to hospital:			
No (%) of episodes	6 (12)	19 (30)	0·01
Mean (SD) duration (days)	2·7 (0·8)	3·8 (2·1)	<0·001
Acute otitis media:			
No (%) of episodes	9 (17)	13 (21)	0·7

the child was admitted to hospital because of severe dyspnoea. There was no significant difference in the incidence of admissions to hospital between highly atopic and other patients (table 3). When the incidence of admission was further analysed using only the IgE concentrations (age matched) as a basis for subgrouping, no significant differences were found in the rate of admission in patients who had high compared with those who had normal concentrations of serum IgE. Nine (36%) of the patients who were admitted were treated with intravenous theophylline and corticosteroids because of progressive dyspnoea despite being given oxygen and nebulised salbutamol inhalation in hospital. Seven of these patients had no virus isolated, and one had rhinovirus, and one coronavirus, infection. One patient was treated in the intensive care unit.

Antibiotics were given during 30 of the total of 115 episodes (26%) (22 for otitis media, four for pneumonia, three for tonsillitis, and one for maxillary sinusitis). The rate of admission to hospital (because of dyspnoea) was similar in patients whether or not they had one of these (probable bacterial) infections—seven of 30 compared with 18 of 85 episodes (23% and 21%, respectively).

LABORATORY FINDINGS

Evidence for an infective agent was found in 52 (45%) episodes, viruses being implicated in 50 and *M pneumoniae* in two. The viruses were: coronavirus (n=22), rhinovirus (n=13), parainfluenza viruses (n=8), adenoviruses (n=8), and influenza A (n=8). Nine patients had two types of viruses during their episodes of respiratory symptoms.

Nasopharyngeal specimens were taken during 97 episodes and in 87 of them (90%) the specimens were taken within 48 hours after the onset of respiratory symptoms. Coronavirus antigen was found in eight patients, all of whom had pronounced increases in their IgG antibodies in follow up serum samples. Influenza A antigen was detected in two samples and adenovirus antigen in one. Virus isolation yielded 12 rhinoviruses and five adenoviruses. From the eight patients in whom influenza A was diagnosed serology showed the presence of viruses in seven; nasopharyngeal swabs had been taken from four patients, and two of the samples were positive by antigen detection test. From the eight patients in whom adenovirus was detected, six were diagnosed by serology and the virus was isolated from three of them; one of these was also positive by antigen detection assay. Two cases were diagnosed solely on virus isolation. Nasopharyngeal specimens had been taken from all eight of the patients with adenovirus infection. All the eight patients with parainfluenza viruses were diagnosed solely by serology despite the fact that antigen was tested in seven of them. Dual infections were found in nine patients.

All these patients had appreciable increases in coronavirus antibodies, and four had also increased influenzae A, two adenovirus, and one parainfluenzae antibodies. Four had coronavirus antigen in the nasopharyngeal secretion and one had influenza A. Adenovirus was isolated from one patient and rhinovirus from one. Fourfold increases in coronavirus OC43 IgG antibodies were found during 20 episodes, and 229E IgG during two.

SYMPTOMS IN DIFFERENT VIRUS INFECTIONS

Episodes of wheezing and fever, and admissions to hospital are shown in table 4. Infections with one or two agents are shown separately. Patients with coronavirus and rhinovirus infections had wheezing attacks lasting 2·4 (1·5) and 4·3 (2·3) days, and were feverish for 3·0 (1·8) and 2·5 (1·7) days, respectively. Seven of the 37 feverish patients (19%) were treated in the hospital because of dyspnoea compared with 18 (33%) who were not feverish. Eighteen of the 25 patients admitted to hospital (72%) had no fever. In 15 of the 25 episodes treated in hospital (60%) the patients had received prophylactic inhalation treatment or theophylline before admission.

When patients from whom viruses had been isolated were compared with those from whom they had not, no significant differences were found in the duration of respiratory symptoms or wheezing (table 5). Patients from whom viruses were not isolated needed significantly more and longer admissions to hospital than those who had a definite virus infection.

Discussion

Asthmatic children have more respiratory infections than their non-asthmatic siblings.[3] During the prospective follow up of three months in the present study of younger patients, 94% of children had rhinorrhea or coughing, or both, on an average of 30 days of the 92 that followed. Laboratory evidence of a viral or mycoplasma infection was found in 45% of these episodes. The retrospective history of the patients also indicated that they had higher incidence of respiratory infections than their age and sex matched controls. The type of day care of the children did not explain this difference, nor did exposure to cigarette smoke or number of siblings.

An appreciable number of wheezy children are atopic,[9 24] 43% in this study. The susceptibility to infections was, however, not related to atopy, confirming the report by Isaacs *et al.*[25] Recurrent upper and lower respiratory infections and wheezing in children are associated with deficient production of interferon alfa,[26] and subclasses of IgG antibodies,[27] which might predispose these children to recurrent infections.

Wheezing occurred in 58% of the laboratory confirmed viral respiratory infections, and in a third of all wheezing episodes the patients needed treatment in hospital. This is in accordance with previous findings in asthmatic children, among whom from 55% to 72% of symptomatic respiratory tract infections resulted in exacerbations of asthma.[28–30] In a recent analysis of 3358 acute asthmatic attacks seen in an emergency room, 26% were admitted.[31]

Carlsen *et al* showed that viruses were the single most common precipitating factor associated with acute asthma in children,[23] and respiratory viruses were diagnosed in 29% of episodes of asthma. In the present study the diagnosis of respiratory infection was confirmed in 40% of wheezing episodes. These two studies differ, however, in that we also studied prospectively those respiratory infections in which the patient did not have wheezing or dyspnoea. In episodes without wheezing viruses were isolated in 56%. This clearly indicates that although viruses are important precipitating factors of wheezy attacks, the outcome of the respiratory infection is variable. The results, although the numbers are small, support the findings of McIntosh *et al* who found that wheezing is less common when the patient has influenza A than in others, like rhinovirus, coronavirus, or parainfluenza infections.[2]

In addition to the type of virus, the development of wheezing might be dependent on other factors including the severity of the infection.[28] Horn *et al* found that the presence of a virus correlated with the severity of the wheezy attack.[4] In the present study, however, viruses were found in only six (24%) of those cases admitted to hospital, and the presence of fever did not increase the risk of wheezing in patients with rhinovirus and coronavirus. These different results might be the result of differences in method, because Horn *et al* found about half of the rhinoviruses only in sputum samples from their patients. This kind of sample could not be collected during this study of younger children.

Although the rate of positive virological diagnosis was high (45%), underdiagnosis of aetiological factors is obvious. This is especially the case in the high incidence of fever (27%) in patients from whom viruses were not isolated. Our effort to isolate viruses was focused on rhinoviruses, and the use of other cell lines might have increased the yield as a number of enteroviruses and herpesviruses do not grow in HeLa cells as used in this study. Traditionally viruses are thought to play a large part in wheezy bronchitis, and therefore the main goal now was virological diagnosis. Bacterial infections are difficult to diagnose in these patients and it is likely that we also underdiagnosed in this regard. Three (23%) of the 13 patients admitted to hospital who were tested had serum C reactive protein concentrations over 40 mg/l, which may suggest the presence of bacterial infection.[32] Based on recent serological findings, 20–24% of patients with acute bronchial obstruction have bacterial or mixed viral and bacterial infections.[33]

Although an appreciable number of the patients were atopic, a diagnosed IgE mediated atopy as such did not seem to increase the risk of wheezing further in these children, confirming the work of others.[23] This result should be interpreted with caution, however, because the highly atopic group was older than the others. It should also be stressed that an appreciable number of children not classified as highly atopic had had some symptoms suggestive for atopy (table 3). By analysis with stepwise regression the most important factors in causing children prone to wheezing to have several wheezing days during the follow up period were smoking at home (as also found by Bisgaard *et al*[34]) and having more than one sibling. The high ranking of the number of siblings might indicate the importance of infections.

Coronaviruses were the most common respiratory viruses found in this study. The incidence of different viruses is naturally dependent on epidemiological factors. This study was conducted during a period when no respiratory syncytial virus was found in the community. One interesting epidemiological finding was that during the coronavirus outbreak in December 1986 (we also found a high incidence at the same time among army trainees), 22 children (41%) had the infection. This indicates a high infectivity rate of these viruses in the community. Reinfection with coronaviruses is common,[35] and in the present study infections occurred even in children who had antibodies to coronaviruses just before the outbreak. In nine laboratory confirmed respiratory infections (17%), evidence of more than one virus was found. In all these episodes there was an increase in coronavirus antibodies, but cross reactions between antigens from other viruses are unlikely because no constant combinations between antibody responses to coronavirus or other virsues were found.

The antiasthmatic prophylaxis (theophylline or steroid or sodium cromoglycate inhalations, or a combination) in 39% of patients might have caused a bias in this study. This is difficult to evaluate because the airway hyper-reactivity in these patients is probably highly variable. It might well be that without prophylaxis some of the patients would have had even more wheezy episodes. Of all the wheezy episodes that required admission to hospital, however, 60% occurred in patients having continuous prophylaxis, which clearly indicates that the prophylaxic used in this group of young patients was not satisfactory.

In conclusion, this study shows that children who are prone to wheezing have a high morbidity from respiratory infections. Although 43% of these children were highly atopic the susceptibility to respiratory infections was not associated with diagnosed atopy. Virus infections were diagnosed in 45% of respiratory episodes but the occurrence of wheezing was not related to the presence of the virus. Wheezing was associated with smoking of the parents at home and having more than one sibling.

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Audit of results of operations for infantile pyloric stenosis in a district general hospital

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Abstract

Because of the proposal that infants with hypertrophic pyloric stenosis should only be treated by surgeons with an interest in paediatric surgery, we carried out a retrospective study to audit our experience in a district general hospital. Forty six infants over a five year period underwent pyloromyotomy. There were no deaths, and 36 infants (78%) made uneventful recoveries. Perforation of the duodenal mucosa occurred during the operation in 11 patients, and eight complications developed in six of these infants. There were seven wound infections, and two patients had vomiting that lasted four days or longer after their operations. There were no long term feeding problems.

The results of this study show that such patients can be successfully treated in district general hospitals, and three areas merit special attention: meticulous surgical technique, the use of prophylactic antibiotics, and early graduated feeding.

In a recent report from a regional centre in London, it was suggested that infants being treated in a district general hospital for hypertrophic pyloric stenosis should instead be treated by surgeons with a special interest in paediatric surgery.[1] An earlier study from a district general hospital in England was cited, and the proposal was made because of the high complication rate.[2] These prompted the present retrospective study: our aims were, firstly, to audit our own experience at a district general hospital in treating infants with pyloric stenosis, and, secondly, to propose any necessary changes in management so that such patients may be successfully treated by general surgeons in district general hospitals.

Patients and methods

During the five year period July 1984 to June 1989, 46 infants with hypertrophic pyloric stenosis were referred for treatment to the department of surgery at this hospital. There were 43 boys (93%) and three girls. The mean age at presentation to hospital was 5 weeks (range 2–14). Although most of the babies had had symptoms of postprandial non-bilious vomiting for a mean duration of six days, four infants (9%) had been ill for three weeks or longer. A family history of pyloric stenosis was present in three cases (mother, maternal aunt and uncle, and paternal uncle), and 24 (52%) were first born children. Four babies were born prematurely, and associated abnormalities were encountered in two: one child had a duplex ureter, and a second had Down's syndrome.

All 46 infants were admitted to the special care baby unit under the care of a paediatrician. On initial examination, 14 infants (30%) were clinically dehydrated (mild, n=6 and moderate, n=8), and they were duly treated with appropriate intravenous fluid replacement. Infants with electrolyte imbalances were also treated. The diagnosis of infantile hypertrophic pyloric stenosis was confirmed clinically in 44 of the 46 infants after a test feed had been given and the pyloric 'tumour' had been palpated. The remaining two infants were diagnosed on clinical ground alone. Plain abdominal radiographs showed a distended stomach (n=2), and barium studies (n=5) were suggestive of gastric outlet obstruction. An ultrasonographic examination was performed in one case before the barium study. After re-examination by the surgical team on call nasogastric tubes were passed in each infant, and the stomach contents aspirated. Operative treatment was planned within the following 24 hours.

All infants underwent operation under general anaesthesia with endotracheal intubation. The operations were carried out by consultant surgeons (n=13), senior surgical registrars (n=19), and post-fellowship registrars (n=14). One preoperative dose of flucloxacillin was given in 32 cases (70%).

In each case a transverse skin incision was made in the right upper quadrant of the abdomen and the diagnosis was confirmed. A longitudinal pyloromyotomy was made with a scalpel with a number 15 blade, and the deepest muscle fibres adjacent to the mucosa were split with a pair of mosquito artery forceps. This procedure was done to minimise the risk of damage to the duodenal mucosa. The integrity of the exposed mucosa was tested in all cases by instilling air through the nasogastric tube. The abdominal wall was closed in layers in 19 infants, and mass closure was used for the remaining 27 (59%). Various suture material were used for closure: polyglactin (n=19), polyglycolic acid (n=12), chromic catgut (n=10), polydioxanone (n=4), and polyamide (n=1). The skin was closed with a subcuticular suture of the same material, except in three infants in whom the skin edges were approximated by an adhesive polyvinyl membrane (Opsite, Smith and Nephew).

The postoperative oral feeding regimen was supervised by the paediatricians and nursing staff in the special care baby unit (table). Feeding started four hours after operation with small sips of Dioralyte (Rorer) and the amount was

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Oral feeding regimen for infants who have had a Ramstedt's pyloromyotomy for hypertrophic pyloric stenosis

Feeding rate	*Feed*	*Amount (ml)*
First 4 hours after operation no feed given then:		
Every hour	Dioralyte*	4
	Dioralyte*	4
	Dioralyte*	8
	Dioralyte*	12
Every 2 hours	Quarter strength milk	15
	Quarter strength milk	20
	Quarter strength milk	30
	Half strength milk	30
Every 3 hours	Half strength milk	45
	Half strength milk	60
	Half strength milk	60
	Three quarter strength milk	75
	Three quarter strength milk	90
Every 4 hours	Full strength milk	90

*Sodium 35 mmol/l, potassium 20 mmol/l, chloride 37 mmol/l, bicarbonate 18 mmol/l, and glucose 200 ml/l.

gradually increased hourly. If the baby vomited, the subsequent amount of feed was not increased. After discharge from hospital each child was followed up at the paediatric and surgical clinics.

Results

The clinical diagnosis of hypertrophic pyloric stenosis was confirmed at operation in all 46 patients, including the two infants in whom the diagnosis had been made on clinical grounds alone. After Ramstedt's pyloromyotomy, 36 infants (78%) made uneventful recoveries, and in 44 infants (96%) vomiting ceased within three days of operation. No child required a repeat pyloromyotomy, and there were no deaths. The median postoperative hospital stay was four days (range two to 12).

The duodenal mucosa was breached during the operation in 11 infants (24%): consultant (n=1), senior registrar (n=5), and registrar (n=5), and in each instance this was repaired with a fine chromic catgut suture. Six of these infants had postoperative complications including vomiting (n=3, in whom it was mild and short lived in two), wound dehiscence (n=2), incisional hernia (n=1), wound infection (n=1), and gaping wound edges after skin closure by Opsite dressing (n=1). Nine of these 11 infants had received preoperative antibiotic prophylaxis, and the mean postoperative hospital stay was significantly longer in this subgroup compared with the remaining patients (7·1 compared with 5·0 days, $p<0{\cdot}02$, Mann-Whitney U test).

Superficial wound infection occurred in seven infants (15%), and *Staphylococcus aureus* was isolated from the wounds in two cases. All infections were mild and none required surgical drainage. In three cases, one dose of antibiotic had been given preoperatively. There were two wound dehiscences, both of which were associated with breached duodenal mucosa. In each case, the wound burst on the second postoperative day, and both infants had had mass closure of the abdominal wall with polyglycolic acid sutures. There was one incisional hernia, which occurred after 25 days; the abdominal wall had been closed in layers with chromic catgut sutures. In three infants, the wound edges gaped and had to be taped with Steri-strips; in two of these children Opsite had been used for skin closure.

Thirteen infants had vomited postoperatively (28%). This was mild and short lived (lasting two or three days) in 11 cases, and lasted four days or longer in two children. In all infants, however, the vomiting settled spontaneously before discharge from hospital. Other complications encountered were urinary tract infection (n=1) and eye infection with *S aureus* (n=1).

The median follow up period was six weeks, and seven children were followed up for longer than two years. There were no long term feeding problems, although two children had mild gastro-oesophageal reflux. Only two infants were slow to gain weight during the follow up period.

Discussion

The number of infants with pyloric stenosis treated each year at this hospital is similar to those from other district general hospitals in England.[2 3] Our incidence compares favourably with the reported incidence of the condition in the Western world of between 1 and 3/1000 live births.[4 5] The number of such patients treated in the layer regional centres is greater, partly as a result of referrals from peripheral hospitals.[1]

The diagnosis is made clinically by the palpation of the hypertrophied pylorus, after a small 'test feed' has been given to the infant. This is facilitated by aspiration of the stomach contents through a nasogastric tube, which is then removed.[6] In the present study, the pyloric 'tumour' was palpated in 44 of the 46 infants (96%), a rate similar to other reports.[1 2 6] The hypertrophied pylorus can be somewhat elusive, however, and multiple examinations are commonly required to locate it. Radiological or ultrasonographic investigations, or both, have been suggested to improve the diagnostic accuracy, but are not routinely performed in these patients. Indeed, the request rate for such examinations in the United Kingdom varies between 6 and 23%.[1–3] This differs from the clinical practice in the United States; it was recently reported that roughly 80% of such infants were referred for one or other diagnostic imaging procedure.[6] The authors concluded that such investigations are unnecessary if the diagnosis can be made clinically. Even in difficult cases where there is clinical doubt, however, barium studies are often equivocal.[7] Ultrasongraphic examination, first performed in 1977 in such patients,[8] is complicated by subjective interpretation, and differing diagnostic criteria have been reported.[9 10] Its use for diagnosis seems doubtful.[1 11]

In the present study, the consultant surgeons, senior registrars, and post-fellowship registrars each carried out similar numbers of operations, but the postoperative complications were slightly more common among patients operated on by the registrars. The duodenal mucosa was performed on 11 occasions, and was associated with eight postoperative complications. Of these eight, however, five were mild (vomiting, wound infection, and gaping wound edges) and the remaining three (wound dehiscence and incisional hernia) were probably related more to the surgical technique than the perforation of the duodenal mucosa. Indeed, in a recent retrospective study, surgical technique was the only variable significantly associated with subsequent wound infection.[12] It is vitally important to recognise a perforation in the duodenal mucosa and to repair it immediately. Mosquito artery forceps were used to prise apart the deepest muscle fibres of the pyloric, but recently the rounded end of the scalpel holder has been reported to be superior in protecting against mucosal perforation.[1]

Almost half of the postoperative complications in the present study were related to the wound. Meticulous attention to the technique of wound closure is essential in order to reduce this incidence. A variety of suture materials was used for abdominal wall closure, although chromic catgut was used only in the early part of the study. Recently, a move has been made towards using polydioxanone rather than the other materials. This suture, when used in a mass closure technique, seems to be effective in preventing wound dehiscence and is associated with a significantly lower wound infection rate.[1 2] Wound dehiscence is more common after operations done under local anaesthetic,[2 3] and this is related to the technical difficulty of closing a wound without adequate muscle relaxation.[1]

The wound infection rate is the present study is comparable with quoted rates of 5–17% from other centres.[1–3 5 12] The umbilicus is an important source of *S aureus* infection, and has been implicated in the aetiology of wound infection.[5 13 14] A preoperative dose of an antistaphylococcal antibiotic was given in almost 70% of our patients and at operation the umbilicus was cleaned with chlorhexidine. Other authors advocate, in addition, sealing off the umbilicus with adhesive tape, but the effect of this in reducing the wound infection rate is limited.[1 13]

Vomiting during the first two postoperative days is common and self limiting.[1–3] It is thought most likely to be the result of inhibition of gastric peristalsis during the first 24 hours after operation, with or without associated gastro-oesophageal reflux.[13] Preoperative oesophagitis and the use of general anaesthesia have also been implicated.[1 2] To circumvent this early vomiting, a delayed feeding regimen was proposed whereby the infants were fasted for the first 24 hours after the operation.[14] As little importance is placed on this early vomiting these patients may be fed orally within the first four hours of operation, and tolerate it well provided that the feeds are introduced slowly.

No patients in the study had any long term feeding difficulties. After a complete pyloromyotomy this is normal, as the hypertrophy at the pyloric regresses at a variable rate and the pylorus achieves a normal size at about 12 weeks after operation.[8] Mild gastro-oesophageal reflux was evident in two children, however, but this is a recognised problem in a small proportion of patients after Ramstedt's pyloromyotomy.

The results of this study show that infants with hypertrophic pyloric stenosis can be successfully treated by general surgeons in a district general hospital. In order to improve our results and more closely match those of regional centres, however, there are three areas that merit special attention: meticulous attention to surgical technique, the use of preoperative prophylactic antibiotics, and gentle and graduated introduction of oral feeding after operation.

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Commentary

An article in this journal in 1988 by Zeidan *et al* reviewed the management of 106 babies with hypertrophic pyloric stenosis.[1] Their patients were admitted under the care of one surgeon working in two children's hospitals: Queen Elizabeth, Hackney, and the Hospital for Sick Children, Great Ormond Street. For those who may have forgotten, the final sentence in the article suggested that, '. . . . healthy infants being treated in district general hospitals should be treated by surgeons and anaesthetists with a special interest in paediatric surgery'. This sentiment prompted the present authors to review experience in their hospital. The preoperative and postoperative management was undertaken by the paediatricians and the surgery was performed by the 'on call' surgical team. There were no operative deaths in either series. However, morbidity rates differed considerably: dehiscence was 0% compared with 4% present series, wound infection 5% compared with 15%, and duodenal perforation 8% compared with 24%. Both series showed a high degree of accuracy of clinical diagnosis and in neither series was postoperative stay prolonged. On the basis of these results, the authors conclude that pyloric stenosis can be successfully managed by general surgeons and by inference by surgeons without a particular interest in the surgery of childhood. They do not discuss whether or not they consider this optimal management.

There are recurrent themes in publications dealing with pyloric stenosis. These relate to diagnostic methods, operative detail, surgical complications, and postoperative management.[2–6]

The diagnosis can be made clinically in over 90% of patients.[1] With the advent of ultrasound diagnosis, however, it seems unlikely that many test feeds will be repeated. It remains to be seen whether ultrasound will prove accurate when the clinical diagnosis is in doubt. Many radiologists will feel more comfortable using a contrast study. Few would agree with a decision to operate on the basis of clinical suspicion alone.

The number of incisions recommended for the operation testify to the fact that none is entirely trouble free. A short, midline epigastric incision is easy to make and to close, and gives a superior cosmetic result to the more common transverse incision. Recent experience with the supraumbilical Bianchi incision suggests that access is no more difficult and the cosmetic result is incomparable.[6] Proximity to the umbilicus may, in theory, increase the risk of infection.

There is general agreement that the pyloromyotomy should remain extramucosal. With a finger invaginating the distal end of the pylorus, an incision is made from the pylorus to the antrum of the stomach. The peritoneum and superficial muscle fibres are divided and the muscle is then spread with a mosquito forceps or pyloric spreader. The tumour splits cleanly along the length of the incision. At the distal end, the split may become oblique, thereby indicating the myotomy is complete at that level. It is unnecessary to divide every fibre and attempts to do so frequently result in duodenal perforation. Having seen the inside of more than one duodenum, I now split the tumour widely and leave the distal end alone. Our experience with repeat pyloromyotomies has shown that the initial operation was usually on the antrum proximal to the tumour. In a few instances, a very short and inadequate myotomy had been performed. Contrary to popular belief, serious haemorrhage can and does occur from the tumour. It is worth waiting a few minutes to ensure that this does not occur.

Wound dehiscence on the second postoperative day is due to suture failure or sutures cutting through. Either way, a change of technique will obviate the problem. Babies with pyloric stenosis seem to have more trouble with their wounds than other neonates or infants. Mass closure using an absorbable suture (other than catgut) seems the best option.[7]

Retrospective reviews do not give a true record of wound infection, particularly those that have occurred outside hospital. The true rate is much higher even when note keeping is obsessional. A recorded rate of 15% is, therefore, of some concern. Surgical technique encompasses many factors. Rao and Youngson (albeit retrospectively) showed that one surgeon's technique resulted in a much lower infection rate (one in 70 patients) than that of his colleagues.[7] Antibiotic usage in the present series was associated with a lower infection rate: 9% compared with 29%.

Postoperative feeding regimens for pyloric stenosis have a long history.[8] No two regimens are the same—a glowing tribute to their overall value. It has been known for many years that gastric peristalsis is abolished for about 24 hours after pyloromyotomy.[9 10] It is acknowledged that there is no rush to operate and the surgery is not performed as an emergency. Postoperative feeding is not an emergency either. Feeding regimens come from a time when venous access was non-existent. There is neither science nor logic in feeding a baby with an inert stomach. Delayed feeding does not delay discharge.[11] My own practice is to introduce full strength feeds 24–30 hours after surgery. In the absence of vomiting, the baby may be discharged at any time thereafter.

The Ramstedt operation is a straightforward procedure and gives excellent results when performed correctly; it is difficult to perform incorrectly. However, there is more to the management of these babies than the pyloromyotomy. In all branches of surgery, good results come from the consistent application of high standards with critical assessment of the outcome. Only then can specific problems be identified and overcome. There seems little point in diluting experience with relatively uncommon conditions like pyloric stenosis. Concentrating the experience in the hands of fewer people would surely improve results. Over a 16 year period, Jacoby, a paediatrician, operated on 104 babies with pyloric stenosis.[12] He had a single duodenum perforation and a single burst abodmen. No patient had a general anaesthetic. Can surgeons really be satisfied with less satisfactory results?

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Longitudinal study of cholesterol values in 68 children from birth to 11 years of age

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Abstract

Sixty eight children born in 1977 who were taking part in an unrelated study of childhood asthma were selected to have their serum cholesterol concentrations measured at birth, and at 4 months and 1, 2, 3, 4, 5, and 11 years of age. Concentrations of high density lipoprotein were measured at 5 and 11 years.

Cholesterol values increased rapidly from birth and plateaued at 1 year. There was a further small rise just before puberty. Tracking of values was seen after the age of 1 year, but did not become established until 4 years of age. The cholesterol concentrations in girls were marginally higher than those in boys. The mean (SD) values of cholesterol (mmol/l) for boys were: at birth, 1·7 (0·4); at 1 year, 3·9 (0·9); at 5 years, 5·2 (1·9); and at 11 years, 5·0 (0·7). For girls the corresponding figures were: at birth, 1·9 (0·6); at 1 year, 4·7 (1·0); at 5 years, 4·6 (0·7); and at 11 years, 5·1 (0·7). The mean (SD) high density lipoprotein concentrations (mmol/l) for boys were: at 5, 1·16 (0·35) and at 11, 1·51 (0·23). For girls they were 1·28 (0·30) and 1·56 (0·27), respectively.

The serum cholesterol concentrations in these children were high compared with published figures from north America.

Coronary heart disease and cerebrovascular disease remain major causes of morbidity and mortality. The World Health Organisation (WHO) report on the prevention of cardiovascular disease concluded that sufficient knowledge had accumulated to achieve a large reduction in its incidence and gave prominence to dietary factors.[1] In the United States there has been a decline in both saturated fat intake and mortality from coronary heart disease but in the United Kingdom change has been slow.[2] The reports of three expert panels (American, European, and British) agree that there is a need to instigate preventive measures in childhood, as they consider that atherogenesis has its origin in childhood and that life styles are also formed during this period.[3]

The present study, initially started to provide 'in house' reference values, may help to explain why British adult cardiovascular mortality remains high.

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Patients and methods

A cohort of 68 children was recruited in 1977 as part of a prospective study of the development of atopy in a group of children all of whom had one atopic parent. No attention was paid to the presence of familial coronary risk factors in this selection, which was made antenatally at the maternity outpatient clinic of Poole General Hospital. The study was approved by the hospital ethics committee. The cohort comprised 31 boys and 37 girls, all but one of whom were white. No attempt was made to modify the children's diet during the study. The social class of the families determined by the paternal employment when the child was aged 5 was: I—13%, II—36%, III—16%, IV—27%, V—6%, and 2% unclassified. This cohort represents the remaining children available for study at age 11 from an original cohort of 95.

The children were seen annually for the first five years of life and at the age of 11 when all except one girl were still prepubertal. Cord blood was obtained at birth and then blood samples were taken when the children were 4 months of age, annually at the time of their birthday during the first five years, and during the spring and summer of 1988. Blood was taken at least two hours after the previous feed; after infancy this was usually a four hour fast and at 11 the children fasted overnight. It was not possible to obtain blood from every child at each age. This was particularly apparent during the preschool period because of parental reluctance to submit their child to a venepuncture.

Cholesterol was measured on single samples by a cholesterol oxidase method at 37°C,[4] using a commercial kit (Boehringer Mannheim, GmbH Diagnostica). At each age quality control against national standards was undertaken.

In the summaries of the Wellcome External Quality Assessment Programme published every six months for the period October 1980 to November 1988, this laboratory's bias for cholesterol did not exceed +0·18 mmol/l compared with the zero reference of all other methods, but tended to be negative for the period up to April 1986 and positive after that. The variation in our method for the period of these tests was not significantly different from that of other laboratories who were using the same method and who participated in the Wellcome Quality Assurance scheme. High density lipoprotein was measured after precipitation by phosphotungstate and magnesium chloride using the cholesterol enzymatic method with suitable standards.[5] The blood had been frozen before assay.

The data were not transformed before statistical analysis, as in larger series, cholesterol values have tended to follow a normal distribution. Correlation coefficients for tracking were obtained by comparing the ranking of measured values at each age and the corresponding rank-

Table 1 Serum cholesterol values (mmol/l)

Age (years)	*Girls*		*Boys*		*All children*	
	No of children	*Mean (SD) cholesterol value*	*No of children*	*Mean (SD) cholesterol value*	*No of children*	*Mean (SD) cholesterol value*
Birth	25	1·9 (0·6)	22	1·7 (0·4)	47	1·8 (0·5)
0·3	26	4·4 (1·0)	23	3·9 (0·7)	49	4·2 (0·9)
1	26	4·7 (1·0)	17	4·5 (0·9)	43	4·6 (1·0)
2	22	5·0 (0·8)	17	4·3 (1·2)	39	4·7 (1·0)
3	18	4·5 (0·9)	14	4·5 (1·0)	32	4·5 (1·0)
4	30	5·0 (0·9)	21	5·0 (0·9)	51	5·0 (0·9)
5	27	4·6 (0·7)	22	4·8 (0·7)	49	4·9 (1·4)
11	36	5·1 (0·7)	30	5·0 (0·7)	66	5·1 (0·7)

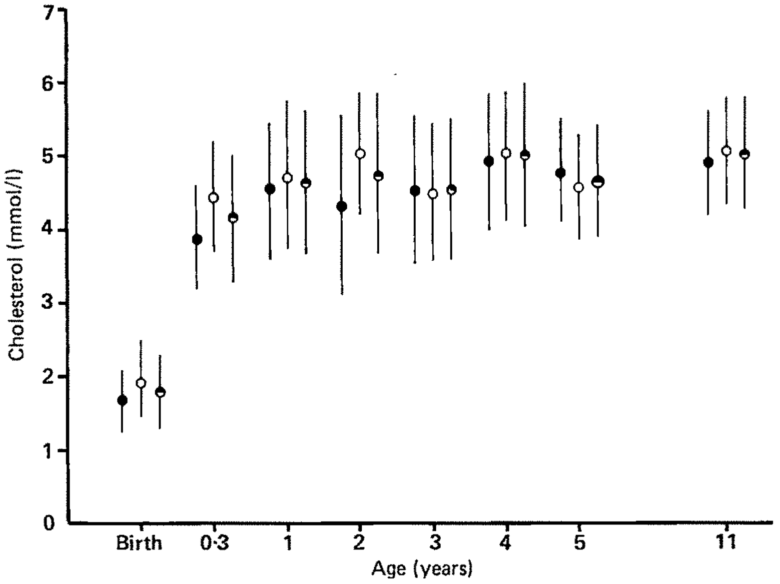

Figure 1 Serum cholesterol values. Solid circles indicate boys, open circles girls, and divided circles total values. Vertical bars represent SD.

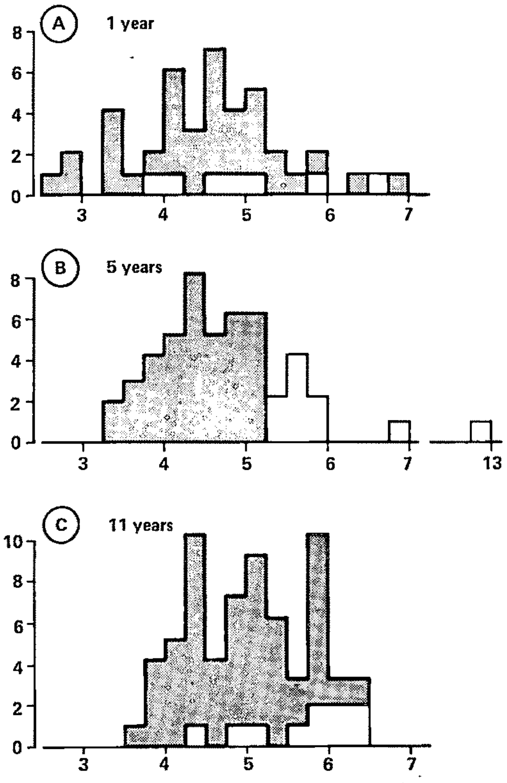

Figure 2 Distribution of serum cholesterol values for total cohort at (A) 1, (B) 5, and (C) 11 years. The open blocks in (B) represent the 10 highest values at 5 years.

ing of those children's values at 11, using Spearman's rank correlation.

Results

The cholesterol values for the cohort are shown in table 1. The year by year variation in numbers is the result of some children declining venepuncture. The sample number, and the arithmetic mean (SD) are shown for different ages (fig 1). The values increased rapidly from birth to 4 months of age and plateaued at 1 year. The mean (SD) of individual changes in cholesterol were: from birth to 4 months 2·3 (0·9), from 4 months to 1 year 0·6 (1·3), from birth to 1 year 2·8 (1·1), from 1 to 2 years 0·1 (0·9), from 2 to 3 years −0·4 (0·8), from 3 to 4 years 0·5 (1·1), from 4 to 5 years −0·1 (0·7), from 5 to 11 years 0·3 (0·6), and from birth to 11 years 3·3 (0·8), respectively. The girls had a higher group mean than the boys. There was no difference in values between children who were atopic (n=35) and those who were not (n=33).

The frequency distributions of cholesterol values at 1, 5, and 11 years are shown in fig 2. A tracking phenomenon was seen for the higher values between the ages of 5 and 11. The children with the highest 10 values at 5 years of age have been picked out and their values at 1 and 11 highlighted. A similar phenomenon was found for the lowest values. The correlation coefficients of ranking among values at birth, 4 months, 1, 2, 3, 4, 5, and 11 years are shown in table 2. A correlation of 1 means that there was perfect tracking of results and 0 that there was none.

High density lipoprotein concentrations at 5 and 11 years are shown in table 3. The mean (SD) of individual changes of high density lipoprotein concentrations between 5 and 11 years was 0·31 (0·4) mmol/l. No tracking was observed between the limited values at 5 and

Table 2 Rank correlation coefficients between cholesterol values in early childhood and those at the age of 11 years

Age (years)	*Girls*		*Boys*	
	Correlation coefficient	*p Value*	*Correlation coefficient*	*p Value*
Birth	0·04	>0·05	0·49	>0·05
0·3	0·31	>0·05	0·57	>0·05
1	0·57	>0·05	0·62	0·05
2	0·25	>0·05	0·47	>0·05
3	0·57	>0·05	0·12	>0·05
4	0·64	0·05	0·74	0·02
5	0·76	0·02	0·66	0·05

Table 3 Serum high density lipoprotein concentrations (mmol/l)

	Age (years)	
	5	*11*
All children:		
No of children	36	66
Mean (SD)	1·22 (0·33)	1·53 (0·25)
Boys:		
No of children	17	30
Mean (SD)	1·16 (0·35)	1·51 (0·23)
Girls:		
No of children	19	36
Mean (SD)	1·28 (0·30)	1·56 (0·27)

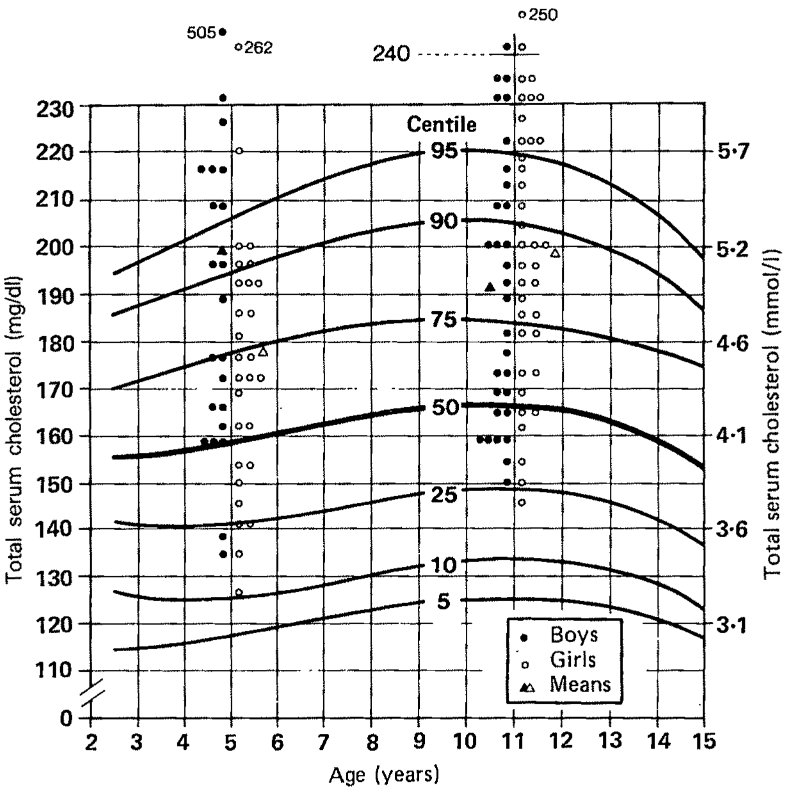

Figure 3 Comparison of cholesterol values in British and American children (British values plotted on American centile chart.[9]

those at 11 years (correlation coefficients 0·17, p>0·05, for boys and 0·35, p>0·05, for girls). The range of cholesterol:high density lipoprotein ratios at 11 years was 2·10:5·74 with an artithmetic mean (SD) of 3·36 (0·39)—boys 3·32 (0·82), and girls 3·4 (0·77), respectively.

Discussion

We know of no published long term longitudinal studies of cholesterol values in children in the United Kingdom. The few cross sectional studies give values in agreement with this study.[6 7 8] When compared with studies from the United States[9 10 11] and Australia[12] our values show similar tracking of values and a slightly higher mean cholesterol value for girls. Cholesterol values rise towards puberty, fall thereafter, and slowly climb to the pubertal values in late adolescence.[13 14 15] One boy had a raised cholesterol value at the age of 5 of 13·2 (high density lipoprotein 1·58); this had been 2·6 at 2, 6·5 at 4, and became 6·3 at 11 (high density lipoprotein 1·30) without treatment or dietary advice.

Our cholesterol values are higher than the normal values published in American series, although this cohort contains a preponderance of girls and an excess of higher social classes, both factors associated with increased values. When plotted on the centile chart from the Bogalusa study, which looked at the total child population in a Louisiana town in the 1970s, our group mean is raised (fig 3).[11] Similar results are obtained when plotted on the Federal Lipid Research Center study centiles.[13] Our high density lipoprotein values are similar with those of the Lipid Research Center study. The ratio of cholesterol:high density lipoprotein is used as an index of risk in adults with a value above 4 causing concern. Our increased cholesterol values are not matched by a corresponding protective increase in high density lipoproteins.

The Lipid Research Center protocol for cholesterol measurement, which is the American standard, uses a non-enzymatic reaction on plasma extract, and is different from the method used in this study.[16] There is always a danger when comparing results obtained using a different method, especially with lipid measurements which are among the most difficult and exacting of laboratory measurements. Our external quality controls are, however, well within United Kingdom standards and we consider comparisons can be made.

There is considerable debate about the concentration of cholesterol desirable for health. The evidence that atherosclerosis begins in childhood was established two decades ago,[17–19] and it seems likely to be a problem of paediatric nutrition. Our cholesterol values would be considered raised by American standards, by which a cholesterol value of 5·18 mmol/l (200 mg/dl) has been suggested as a threshold above which dietary manipulations are indicated.[20] If this is applied to our cohort of 'normal' children 42% would require dietary treatment.

We consider that these differences in results are a cause for concern, and may explain some of the differences in adult mortality resulting from coronary heart disease. The previous position in this country of not recommending treatment limits and accepting raised concentrations in the general population needs to be reconsidered.[21] It seems likely that our raised values are the result of dietary factors. Experience from the United States shows that adult eating habits can be beneficially altered by public education. We suggest that these measures should be applied to the whole family, including the children.

We thank Mrs Joan Wignall for long term nursing support. Dr R Sporik and Mrs Joan Wignall were supported by a grant from the Asthma Research Council.

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Dexamethasone in meningitis

Dr McCracken and his disciples in Dallas have produced impressive evidence that locally acting mediators of inflammation do a fair amount of mischief in bacterial meningitis and their production can be suppressed by giving dexamethasone.[1] In a recent report (Mustafa *et al*, *American Journal of Diseases of Children* 1990;**144**:883–7) they showed that patients with bacterial meningitis treated with dexamethasone (89% due to *Haemophilus influenzae)* had, after 18 to 30 hours, lower cerebrospinal fluid concentrations of prostaglandin (PGE_2), interleukin 1β, and lactate and subsequently fewer neurological sequelae.

The Committee on Infectious Diseases of the American Academy of Pediatrics has given recommendations (*Pediatrics* 1990;**86**:130–3). They conclude, however, that available data is insufficient to make recommendations about children under the age of 2 months or about bacterial meningitis not caused by *H influenzae*.

Dexamethasone should not be used in non-bacterial meningitis. For *H influenzae* meningitis the committee calls for more studies and sits on the fence—'dexamethasone *probably* reduces the likelihood of deafness' (my italics) and 'we recommend individual consideration of dexamethasone . . . after the physician has weighed the benefits and possible risks'. In other words, make your own mind up. If you're going to give it you have to give it at the start, it's illogical to give it after you've thought about it for a few hours, by then you'll have missed the boat, assuming that there is a boat to be caught. Published data suggest that children with a milder illness stand to benefit as much as those with severe disease so there seems to be no point in restricting dexamethasone to severely ill children only. Either you give it or you don't, but don't give it in viral meningitis.

ARCHIVIST

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Severe hypophosphataemia during binge eating in anorexia nervosa

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Abstract

A patient presented with severe hypophosphataemia that had been precipitated during binge eating. It was corrected by restricting the binges, and by hyperalimentation through a duodenal tube together with intravenous supplementation with sodium phosphate for a short period. Phosphate concentrations should be monitored in patients with severe anorexia complicated by bulimic episodes.

A low serum phosphate concentration is a complication that has been recorded in several conditions, including hyperalimentation by intravenous fluids deficient in phosphate,[1 2] alcohol withdrawal, diabetic ketoacidosis, recovery after extensive burns, and refeeding of malnourished prisoners of war. In anorexic patients hypophosphataemia has been noted during both intravenous hyperalimentation and oral refeeding (when the patients were starved but using laxatives). In some anorexic patients hypophosphataemia may have played a part in the deaths of patients who were treated with intravenous hyperalimentation without phosphate supplementation.

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Results of biochemical and haematological investigations

Sodium	142 mmol/l
Chloride	100 mmol/l
Potassium	4·7 mmol/l
Blood urea nitrogen	16·4 mmol/l
Creatinine	62 μmol/l
Total protein	67 g/l
Glucose	6·0 mmol/l
Aspartate aminotransferase activity	18·8 U/l
Calcium	2·37 mmol/l
Phosphate	1·49 mmol/l
Haemaglobin	127 g/l
Packed cell volume	0·40 with 12×10^{-3} reticulocytes
Erythrocyte sedimentation rate	11 mm in first hour

Case report

A white girl aged 16 years old, 160 cm in height, had started dieting at the age of 11 years, and was admitted to hospital several times. Her admission to our adolescent's ward (weighing 26 kg) was her sixth admission. She had eaten practically nothing except for some unsweetened biscuits, white low fat cheese, and vegetables, and drunk coffee with saccharin. She considered herself fat and wished to weigh 23 kg. She also said that she was using large quantities of laxatives.

On admission she was emaciated and severely cachetic, and complained of feeling cold. Her blood pressure was 80/45 mm Hg and did not change when she stood up, her pulse rate was 50–64/minute and temperature 36°C. Her skin was dry and scaly. Initial biochemical values were within the reference range (see table). Urinalysis gave normal results.

During the third week in hospital she started binge eating of large quantities of food from every possible source. Her phosphate concentrations dropped abruptly to 0·13, 0·16, and 0·26 mmol/l consecutively. She was placed on a 7·52 MJ diet comprising three meals and three snacks. Her eagerness to binge forced us to restrain her freedom, to feed her through a duodenal tube, and give her sodium phosphate intravenously. Even after she had been tied to her bed, she persuaded her room mates to bring her food, and even succeeded in pulling out the nasal tube and sucking it directly. Her extreme aggression necessitated antipsychotic drug treatment. She gradually became calmer and we were able to start oral feeding. Her weight was restored and she was discharged from our ward weighing 39 kg.

Follow up consultations took place twice a week. All her biochemical values including phosphorous remain within the reference ranges. Because of her anorexia, however, we are pessimistic about her prognosis.

Discussion

Phosphorus is essential to the body's energy and storing mechanisms,[1–4] and it plays a part in carbohydrate, fat, and protein metabolism. In addition, it is necessary for the structure of the phospholipids composing cell membranes and intracellular organelles of muscle and nerve tissue.[5]

Hypophosphataemia can produce the clinical signs of ATP deficiency or cellular hypoxia affecting the neuromuscular, cardiopulmonary, haematological, gastrointestinal, renal, endocrinological, and skeletal systems.[6 7] It is a rare clinical entity. The daily requirement is 800–1000 mg of elemental phosphorus. Dietary sources include eggs, milk, poultry, cheese, nuts, and vegetables. The kidney reabsorbs up to 90% of phosphorus and stool losses are small, being 100–200 mg/day.[3] This patient by avoiding practically all food while resorting to laxative abuse reduced her phosphate intake and increased her faecal excretion.

Serum phosphate concentrations reflect only a small proportion of total body phosphorus because 99% of phosphate is intracellular.[8] Although within the reference range on admission, her serum phosphate concentration apparently fell precipitously after her binges, thus showing that her total body phosphorus was depleted by her fasting and laxative abuse.

The neurons, red blood cells, and cardiac muscle are particularly vulnerable to ATP depletion.[6 9] Presumably the phosphate supplying these tissues from the serum was just adequate during the periods of nutritional deprivation and the catabolic state. The severe bulimic phase changed her body metabolism from a catabolic to an anabolic state, creating an abrupt demand by her liver and muscles for more phosphate for the production of the phosphorylated intermediates required by glycolysis, glycogen formation, and protein synthesis.[1]

Phosphate then shifted rapidly from her serum into her muscle and liver.[1] [4] The drop in serum phosphate threatened to deprive her nervous system, red blood cells, and heart of their phosphate requirement, creating a metabolic emergency.

Hypophosphataemia is a well known cause of death in anorexic patients who are receiving phosphate deficient intravenous hyperalimentation,[2] and has also been reported in a patient who had been refed orally.[1] Normal serum concentrations do not exclude the existence of dangerous total body phosphate depletion. We suggest that all binging anorexic patients should have their serum phosphate concentrations monitored and adequate phosphate supplementation should be given. If serum phosphorus concentrations start to drop, the patient should be restrained in bed by all legitimate means to stop her having binges and subsequently misusing laxatives and inducing vomiting.

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Measles and vitamin A

Firmly in Michael Caine's 'not many people know that' category is the fact that nearly 60 years ago a paper in the *British Medical Journal* pointed to vitamin A having a protective effect in measles.[1] In 1987 the World Health Organisation recommended vitamin A supplements for children with measles in areas where vitamin A deficiency is rife and where measles has a high mortality.[2]

A recent report from Cape Town (Hussey and Klein, *New England Journal of Medicine* 1990;**323**:160–4) confirms the beneficial effect of vitamin A in severe measles. Altogether 189 children entered a randomised controlled trial receiving either vitamin A 400 000 IU or placebo orally. Mortality was 10·3% in the placebo group and 2·2% in the vitamin A group. In the supplemented children the duration of pneumonia was halved and that of diarrhoea reduced by a third. Complications such as post measles croup and herpes stomatitis were significantly reduced.

Measles kills about 2 million children a year so this work is clearly of immense importance especially in developing countries, but low serum concentrations of vitamin A are known to occur during measles even in populations not known to be deficient in the vitamin and the authors therefore advocate giving the supplement to any child who has severe measles.

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Mineral balance in infantile cortical hyperostosis: effects of corticosteroids

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Abstract

The effects on mineral metabolism of therapeutic doses of corticosteroids were investigated in infantile cortical hyperostosis; in four untreated cases the calcium, phosphorus, and magnesium balances were strongly positive. In one severe case, treatment with prednisolone was associated with an alteration to negative calcium and magnesium balance, and faecal losses of calcium were particularly high. This effect persisted for at least three months after the steroids had been discontinued, and during this period there was pronounced retardation of linear growth. Six months after the treatment had been stopped mineral balance was again positive and there was rapid 'catch up' in growth.

In infancy, the negative effect of corticosteroids on calcium, phosphorus, and magnesium metabolism may contribute to inhibition of bone growth and steroid stunting.

We know of few biochemical studies in infantile cortical hyperostosis. Serum calcium and phosphorus concentrations are normal but alkaline phosphatase activity is usually increased during the active phase.[1] Aminoaciduria has been reported in one case.[2]

Corticosteroid treatment has been advised with reservation[3 4] but recommended for all patients,[1 5] particularly for severe cases.[6] In this study of infantile cortical hyperostosis one case, whose growth was studied longitudinally, had a series of balance studies for calcium, phosphorus, and magnesium before, during, and after treatment with corticosteroids. Three other cases not receiving steroids had single balance studies.

Patients and methods

Clinical details of the four infants are shown in table 1. Case 1 had generalised disease and was seriously ill; a protracted course of corticosteroid was therefore necessary. Case 2 had generalised disease, and cases 3 and 4 had disease localised to the mandible that resolved without the need for steroids.

Balance studies, except where stated, all extended over five day periods. Analysis for calcium, phosphate, and magnesium was made on duplicate diets, stools, and urine. Samples were homogenised and aliquots were digested in dilute nitric acid. Calcium and magnesium were estimated by atomic absorption spectrophotometry and phosphate by a micro adaptation of the phosphomolybdate method of Fiske and Subbarow.[7]

Results

In all four patients serum calcium, magnesium, and phosphorus were always within normal limits and there was no evidence of acid-base disturbance, hepatic, renal glomerular, or tubular dysfunction.

Changes in linear growth in case 1 are shown in fig 1. Height is shown as the difference between the observed value and the normal mean height for that age expressed as a proportion of the normal SD for that age (SD score). Balance data in the four cases are shown for calcium, phosphorus, and magnesium in tables 1, 2, and 3, respectively. Sequential balance data for case 1 are shown diagrammatically in fig 2.

When untreated (case 1, balance (i); cases 2, 3, and 4) gross retention of calcium was high for age and also in relation to intake.[8 9] This excessive retention was especially pronounced in

Table 1 Calcium balances

	Age (months)	*Weight (kg)*	*Intake (mmol/day)*	*Output (mmol/day)*		*Gross retention (mmol/day)*	*Comment*
				Faeces	*Urine*		
Case 1:							
Balance (i)	3·5	4·9	28·7	18·6	0·6	9·5	Clinical onset aged 10 weeks Generalised disease One week before steroids started
Balance (ii)	5	5·1	24·0	20·95	0·2	2·85	Prednisolone 10 mg/day for one month
Balance (iii)*	6·5	5·9	18·7	18·5	0·7	−0·5	Prednisolone 10 mg/day for two months Off steroids for two weeks ACTH 20 IU daily in week 1, three times in week 2, and twice in week 3
Balance (iv)	10	7·1	8·4	8·7	0·4	−0·7	Off treatment for three months
Balance (v)	14	8·7	11·1	5·2	0·1	5·8	Six months after end of steroid treatment
Case 2	4·5	5·9	19·0	9·1	0	9·9	Clinical onset aged 9 weeks Generalised disease; relapse at age 4 months
Case 3	4	6·8	21·5	12·2	0·9	8·4	Clinical onset aged 11 weeks Localised disease
Case 4	5	5·6	17·7	10·0	1·4	6·3	Clinical onset aged 4 months Localised disease

*Three day balance period, all others five day periods. ACTH, adrenocorticotrophic hormone.

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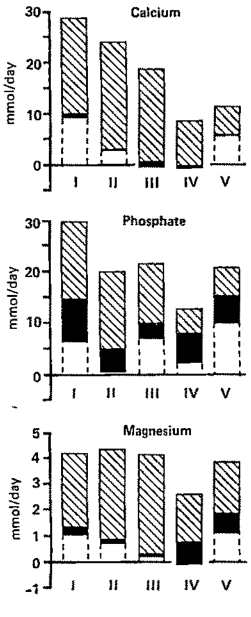

Figure 2 Sequential mean 24 hour mineral balances in case 1. Intake is shown by the upper limit of the enclosed block from the base line. Excretion is represented by the distance between the upper and lower limits of the enclosed block. Urinary excretion is represented by the solid shading of the enclosed block, and faecal excretion is shown by the diagonal shaded portion of the enclosed block. Mineral balance is thus the distance between the lower limit of the enclosed block and the base line and is positive when the lower limit of the enclosed block is above the line and negative when it is below.

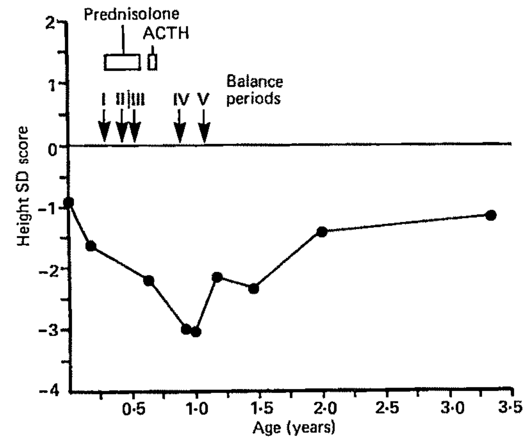

Figure 1 Changes in linear growth in case 1 in relation to balance periods and treatment. (ACTH, adrenocorticotrophic hormone.)

Table 2 Phosphorus balances

	Intake (mmol/day)	*Output (mmol/day)*		*Gross retention (mmol/day)*
		Faeces	*Urine*	
Case 1:				
Balance (i)	29·5	15·2	6·7	7·6
Balance (ii)	19·2	14·7	3·9	0·6
Balance (iii)*	21·4	11·6	2·9	6·9
Balance (iv)	12·5	4·4	6·0	2·1
Balance (v)	20·6	5·2	5·4	10·0
Case 2	19·5	5·9	7·8	5·8
Case 3	27·7	17·4	8·1	2·2
Case 4	21·0	11·4	7·6	2·0

*Three day balance period, all others five day periods.

Table 3 Magnesium balances

	Intake (mmol/day)	*Output (mmol/day)*		*Gross retention (mmol/day)*
		Faeces	*Urine*	
Case 1:				
Balance (i)	4·2	2·9	0·3	1·0
Balance (ii)	4·4	3·6	0·1	0·7
Balance (iii)*	4·2	3·9	0·1	0·2
Balance (iv)	2·6	1·9	0·8	−0·1
Balance (v)	3·9	2·0	0·8	1·1
Case 2	3·1	1·5	0·2	1·4
Case 3	2·8	2·2	0·2	0·4
Case 4	2·9	1·9	0·4	0·6

*Three day balance period, all others five day periods.

cases 1 and 2 who had widespread disease. Gross retention of phosphate was high in case 1, but near normal for age and intake in the other cases.[8] [9] Phosphate retention was low in relation to calcium retention. Gross retention of magnesium was high in cases 1 and 2, and normal in cases 3 and 4.

The effect of treatment with corticosteroids was shown in case 1. After one month, gross retention of calcium had fallen to one third of the presteroid value, mainly because of an absolute and proportional rise in faecal calcium. The change became more pronounced (balance (iii)), creating negative balance that progressed after steroids had been discontinued until balance (iv) when, three months after stopping treatment, faecal calcium was greater than calcium intake and pronounced negative balance resulted. Six months after corticosteroids had been stopped the calcium balance was again strongly positive.

Changes in phosphate balance were less pr nounced and consistent, but magnesium rete tion fell progressively and balance became neg tive at the time when calcium retention w lowest. Urinary magnesium seemed to rise this stage, although in magnesium deprivatic there is usually renal conservation.[10]

Discussion

The metabolic balance data presented he show that untreated infants with cortical hype ostosis are in strongly positive mineral balanc

Balance is usually positive in infancy with net retention of calcium of about 5 mmol (2(mg)/day to allow for accretion into the growi skeleton.[8] Anything less than this implies a n deficit of calcium, and balances that actual become negative (case 1 balances (iii) and (i indicate a serious degree of mineral depletio

The general tendency to positive balance cases 2, 3, and 4—and in case 1 the strong positive balance before and after treatment- suggest that corticosteroids were indeed respo sible for the change to negative mineral balan that occurred in case 1.

The main reason for this negative calciu balance seemed to be an increase in faec losses. This effect persisted for months aft treatment had been stopped, suggesting son profound functional alteration in intestin mechanisms of absorption or excretion. T tendency for faecal calcium to exceed calciu intake might indicate a state of calcium leaka into bowel ('calcium losing enteropathy').

Urinary calcium in cases 1, 3, and 4 w within the reference range,[8] but in case 2 no c cium was detected in the urine over a five d period, and at other times values of 0·025 mm and 0·15 mmol/day were obtained. In this ca serum calcium tended to be near the lower lir of the reference range; as a result tubular rea sorption of calcium may have been enhanced the effect of secondary hyperparathyroidis The aminoaciduria reported in Caffey's disea by Campbell and Turner was renal in type, al suggesting an effect on tubular function.[2]

The relationship between the changes mineral balance and the growth retardation case 1 is uncertain, as the effects of treatme cannot be entirely separated from the effects the disease. Negative balance coincided wi maximum depression of linear growt however, and a reversion to positive balan correlated with the period of 'catch up' growt Prolonged courses of large doses of cortic steroids lead to stunting with impairment bone growth and delayed skeletal matu tion,[11] [12] but the pathogenesis of these effe remains uncertain.[13] [14] Among contributi factors, the adverse effects of corticosteroids mineral metabolism and bone have been sho in children,[15–17] and direct correlation sho between the degree of osteopenia and t extent of growth retardation.[18] The report effects of corticosteroids on bone include inhil tion of collagen synthesis,[14] decreased oste blastic activity,[19] and osteopenia.[17] [18] [20]

Calcium depletion complicating treatm with steroids in children has be described.[15, 16] Inhibition of intestinal calcium transport,[21] calciuria,[22] reduced production of 1,25 dihydroxyvitamin D,[23, 24] depletion of circulating 25-hydroxyvitamin D,[25] or antagonism to the effects of vitamin D,[26, 27] have all been implicated. Vitamin D seemed to enhance catch up growth after courses of steroids in rats treated with cortisone.[28]

During rapid development of the skeleton in infancy, the side effects of steroids on linear growth and mineral metabolism might be especially undesirable.

This study suggests that mineral depletion by corticosteroids may be severe and prolonged in infancy contributing to the inhibition of bone growth. Mineral supplements, with or without vitamin D, might help to offset these mineral losses and mitigate the stunting effects of steroids.

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Orocaecal transit time in Duchenne muscular dystrophy

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Abstract

Smooth muscle degeneration may occur in Duchenne muscular dystrophy. We measured fasting orocaecal transit time in patients with advanced Duchenne muscular dystrophy and other muscular dystrophies and in healthy controls. No significant differences were found. In contrast to reports of gastric hypomotility in Duchenne muscular dystrophy, we found no evidence of impaired small intestinal motility.

Although the predominant manifestations of Duchenne muscular dystrophy relate to skeletal and cardiac muscle, gastrointestinal smooth muscle may also be involved.[1–3] Severe and even fatal cases of acute gastric dilatation and intestinal pseudo-obstruction have been reported and associated with histological evidence of smooth muscle fibrosis throughout the gastrointestinal tract.[1–3] To determine whether or not significant dysfunction of gastrointestinal motility occurs, we used the lactulose breath hydrogen test to measure orocaecal transit time[4] in patients with advanced Duchenne muscular dystrophy and other neuromuscular disorders.

Subjects and methods

The lactulose breath hydrogen test was performed in three study groups. (1) This group comprised 10 patients with Duchenne muscular dystrophy who were confined to a wheelchair; their mean (SD) age was 17·0 (1·8) years, range 15–20. (2) This group comprised 10 patients (seven boys) with other neuromuscular disorders (congenital muscular dystrophy (n=3), limb girdle muscular dystrophy (n=3), spinal muscular atrophy type II (n=3), and hereditary motor and sensory neuropathy (n=1)); they were aged 14·5 (3·0) years, range 9–20. (3) This group comprised 10 healthy volunteer controls (six boys) who were aged 19·8 (8·4) years, range 12–37. One patient with Duchenne muscular dystrophy and two with other neuromuscular disorders required regular enemas because of constipation. The others had no gastrointestinal symptoms. The study protocol was approved by the hospital ethics committee and informed consent was obtained from each subject and/or guardian. No subject had received antibiotics for two weeks or laxatives for three days before being studied.

After a 12 hour overnight fast each subject ingested 13·4 g of lactulose (20 ml of Duphalac, Duphar) made up to 200 ml with water. Subjects blew into a collecting system with two bags that filled sequentially. The dead space air was trapped in the first bag; samples of end expiratory (alveolar) air were taken from the second bag for determination of hydrogen concentration using a Model 12 MicroLyzer (QuinTron Instrument Company) calibrated before each use with a standard gas. Samples were collected twice for baseline determination before lactulose administration and every 10 minutes thereafter for at least 120 minutes. Orocaecal transit time was defined as the time to a sustained rise of hydrogen concentration ≥10 ppm above baseline.

Results

The lactulose breath hydrogen test was performed uneventfully in all subjects. A typical study is illustrated in fig 1. Breath hydrogen concentration rises when lactulose reaches the caecum where it is fermented by the colonic flora producing hydrogen, which is absorbed and excreted by the lungs. One subject in each of the three study groups exhibited an early transient hydrogen concentration peak preceding a later sustained rise (fig 1, lower graph). An early peak may result from fermentation of ingested carbohydrate by the oropharyngeal flora,[5] or may be a sign of small bowel bacterial contamination.[6] The magnitude of the early rises in these three subjects (21, 29, and 32 ppm) is more suggestive of bacterial overgrowth, although none had any related symptoms.

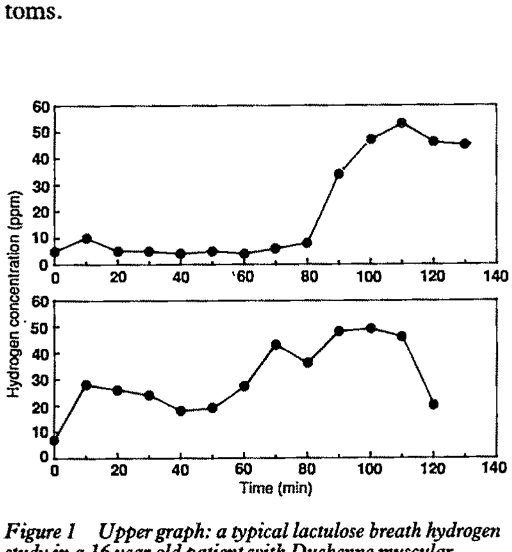

Figure 1 Upper graph: a typical lactulose breath hydrogen study in a 16 year old patient with Duchenne muscular dystrophy showing an orocaecal transit time of 90 minutes. Lower graph: lactulose breath hydrogen study in a 16 year old patient with Duchenne muscular dystrophy with an early peak at 10 minutes indicating bacterial overgrowth and a secondary rise at 70 minutes representing the orocaecal transit time.

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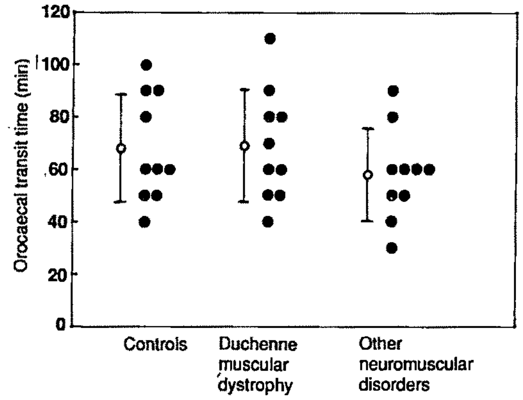

Figure 2 Orocaecal transit time in 10 control subjects, 10 Duchenne muscular dystrophy patients and 10 patients with other neuromuscular disorders. Vertical bars to left of each group indicate mean (SD) values.

Mean (SD) orocaecal transit time was 68·0 (20·4) minutes in controls, 69·0 (21·3) minutes in the patients with Duchenne muscular dystrophy, and 58·0 (17·5) minutes in the patients with other neuromuscular disorders (fig 2). There was no significant difference between the groups (p=0·55, Kruskal-Wallis test).

Discussion

Despite postmortem evidence of significant gastrointestinal smooth muscle degeneration in Duchenne muscular dystrophy,[1–3] little attention has been paid to studying its functional consequences. Barohn *et al* recently documented gastric hypomotility in Duchenne muscular dystrophy patients and postulated that it may be related to a deficiency of dystrophin, the gene product of the Duchenne muscular dystrophy locus.[3]

We found no evidence of delayed fasting orocaecal transit time in either Duchenne muscular dystrophy or other neuromuscular disorders. Our results do not exclude the possibility of delayed gastric emptying in our patients. The orocaecal transit time as measured by the lactulose breath hydrogen test is dependent solely on small intestinal transit time and is not influenced by gastric emptying time.[4 7] This is because orocaecal transit time is determined by the time taken for the head (rather than the bulk) of the lactulose column to reach the caecum. Even if gastric emptying is significantly delayed, a small amount of lactulose will still pass through the pylorus almost immediately after ingestion.

There is no uniformly accepted methodology for determination of orocaecal transit time using the lactulose breath hydrogen test. We measured it using a solution of lactulose in the fasting state only. This straightforward method has been successfully used to demonstrate the influence on intestinal transit of various states such as cystic fibrosis,[8] thyroid disease,[9] and aerobic exercise.[10] Determination of postprandial orocaecal transit time using standard liquid[11] or solid[12] meals has been shown to improve the reproducibility of the test. We cannot exclude the possibility that subjects with Duchenne muscular dystrophy may have an abnormality in small intestinal motility detectable only in the postprandial state.

The apparent discrepancy between our finding of normal small intestinal motility in contrast to the gastric hypomotility in Duchenne muscular dystrophy described by Barohn *et al* is unlikely to be due to a difference in the patients studied[3]; the mean age of both groups was almost identical, and all of our patients were confined to wheelchairs. A more likely explanation supported by histological findings from postmortem studies is that the degenerative process predominantly affects the upper gastrointestinal smooth muscle.[3]

Some patients with Duchenne muscular dystrophy suffer from constipation. Our findings suggest that the constipation is not due to impaired small intestinal motility. Colonic motility, another possible factor in the genesis of constipation, has not yet been studied in Duchenne muscular dystrophy. Most likely, however, the constipation in these patients is related to their immobility and weakness of their abdominal wall musculature.

Despite our finding of normal fasting small intestinal transit time, we cannot exclude the presence of small intestinal smooth muscle degeneration in our patients as such changes have been demonstrated at postmortem examination in the absence of overt clinical symptoms.[1] We can, however, conclude that we have found no evidence for impairment of small intestinal motility even in advanced Duchenne muscular dystrophy.

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Effects of maternal iodine supplementation during pregnancy

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Abstract

Reduced maternal thyroid hormone concentrations during pregnancy can adversely affect fetal neurological development. In the context of national iodine supplementation programmes, concern has been expressed over the theoretical possibility that iodine supplementation during pregnancy might adversely affect fetal development as a result of maternal thyroid inhibition from the Wolff-Chaikoff effect. In a double blind controlled trial in five villages in Papua New Guinea, several measures of motor and cognitive function showed no significant differences at either age 11 or 15 years between those children whose mothers had received supplementary iodine during pregnancy and the control children whose mothers had received the placebo.

Iodine deficiency is a worldwide problem that leads to clinical goitre and the syndrome of endemic cretinism together with subclinical deficits of motor and cognitive function. This spectrum of defects has been collectively labelled iodine deficiency disorder.[1] Prevention of iodine deficiency disorder by iodine supplementation is known to be effective but, in the case of endemic cretinism, supplementation must be before conception because the neurological damage due to iodine deficiency appears to occur early in fetal development.[2] Because iodine supplementation is a relatively cheap and highly effective preventive measure, national programmes of iodine supplementation have been initiated in several countries where iodine deficiency disorder show high prevalence rates. One method of supplementation has been the use of a single dose of iodinated oil by either oral or intramuscular administration. When a single dose is used, the quantity given is substantial, although absorption is slow. The iodine concentration in the oil is approximately 475 mg/ml and doses of up to 5 ml have been used.[3] Failure of normal fetal neurological development attributed to maternal iodine deficiency is thought to be mediated through a reduction of maternal thyroid hormone concentrations and specifically maternal thyroxine.[4-6] Excess iodine administration may lead to an acute inhibition of the thyroid, a phenomenon termed the Wolff-Chaikoff effect after the workers who originally described it.[7] Concern has therefore been raised that administration of iodine during pregnancy may also affect fetal neurological development if it leads to maternal thyroid gland inhibition by the Wolff-Chaikoff effect.[8] This anxiety has imperilled some national iodine prophylactic programmes.

During 1966 a double blind controlled trial using a single dose of intramuscular iodinated oil was carried out in the Western Highlands of Papua New Guinea. In the course of this trial several pregnant women were given iodine at various gestational stages. We report here a long term follow up of these pregnancies using measures of mental and motor function to assess the development of the children.

Methods

The organisation of the controlled trial initiated in the autumn of 1966 has been described previously.[2] In 1978 a follow up was carried out of the cohort of children born to the trial group. The children of mothers who had received iodinated oil constituted the test groups and those of mothers who had received the placebo of physiological saline constituted the control group. Those children born within 40 weeks of the mother receiving either iodinated oil or saline are the index cases for this report. In these cases the mother was assumed to have conceived before the iodinated oil or saline was administered. In 1978, when the index children were approximately 11 years old, several measures of physical and motor performance were applied. These included grip strength, speed of movement, unimanual accuracy, and bimanual accuracy. The methods of carrying out these tests and the scoring procedures have been described previously.[9] For all these measures except that involving the application of screws to bolts the score correlates positively with level of skill—that is, the higher the score the greater the skill. The screwing task was a timed measure and therefore correlates negatively with manual dexterity—that is, the lower the score the greater the dexterity.

In 1982, when the children were approximately 15 years old, a further series of measures of motor and cognitive ability were applied. Some of the unimanual and bimanual measures of manual dexterity used in 1978 were repeated because they had been found to discriminate well for motor performance.[9] In addition, a further test of motor skill was employed that required the subject to transfer a series of 10 one cm pegs from one set of holes in a frame to another set 20 cm away in the frontal plane. The time required for the transfer was measured with a stopwatch. Five repetitions with each hand were made and the score used in the analysis was the mean time required to transfer

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10 pegs. (The shorter the time taken the greater the skill.) In 1982, an attempt was also made to assess the intellectual performance of the children using the Pacific design construction test (PDCT) developed by Ord and used in Papua New Guinea to select army recruits and young people for technical training.[10] The test comprises 13 designs of varying complexity printed on cards. The subject is required to make a copy of each design in tiles (red, white, and red and white) in a set of specially shaped trays. The score is based upon producing correct copies within defined time periods. A preliminary trial of children from the study area, but who were not themselves part of the index sample, showed that they experienced great difficulty in translating the printed design into a model made from the tiles. This difficulty probably reflects their unfamiliarity with pictures. The testing procedure was therefore modified in the following way. The examiner constructed the design tiles in one tray while the subject watched. The subject was then invited to reproduce the design in an adjacent tray. The model was available to the subject throughout the trial. The test was administered in a manner that relied largely on non-verbal instructions though these were supplemented by verbal instructions translated into pidgin English for use in the field.

Standing height was measured using a Harpenden portable anthropometer.

Statistical comparisons of the two groups of children were made using Student's *t* test.

Results

The original 1966 trial was carried out in 27 villages and involved approximately 8000 individuals in each of the test and control groups.[2] Subsequent follow up of the children born into the trial population had to be limited to a more confined group of villages for logistic reasons only. In 1978 and 1982 the follow up was limited to five villages.

Table 1 compares the scores achieved by the two groups of children in 1978 when they were 11 years old. In none of the measures of motor

Table 1 Comparison of scores for test and control groups in 1978

Motor competence measure	*Test (iodinated oil)*		*Control (placebo)*		*Difference between means (95% confidence intervals)*	*p Value*
	No	*Mean (SE)*	*No*	*Mean (SE)*		
Grip strength:						
Right hand	12	11·8 (0·6)	17	12·4 (0·7)	−0·6 (−2·5 to 1·3)	0·46
Left hand	12	11·4 (0·5)	17	11·9 (0·6)	−0·5 (−2·1 to 1·1)	0·59
Speed of movement:						
Taps						
Right hand	12	37·9 (1·8)	18	37·3 (2·1)	+0·6 (−4·9 to 6·1)	0·82
Left hand	12	35·4 (1·7)	18	36·3 (2·2)	−0·9 (−6·5 to 4·6)	0·76
Dots (mean of four trials)	12	21·6 (0·8)	18	21·8 (1·2)	−0·2 (−3·0 to 2·6)	0·89
Bimanual accuracy:						
Beads	11	17·2 (1·0)	17	15·3 (0·9)	+1·9 (−0·8 to 4·6)	0·17
Unimanual accuracy:						
Pegs	12	23·3 (1·4)	18	20·5 (1·2)	+2·8 (−0·9 to 6·5)	0·15
Screws	12	71·9 (7·3)	17	80·8 (10·1)	−8·9 (−34·0 to 16·2)	0·48

The differences between mean test results are positive or negative and the meaning of directional changes for each test is explained in the text.

Table 2 Comparison of scores for test and control groups in 1982

Motor competence measure	*Test (iodinated oil)*		*Control (placebo)*		*Difference between means (95% confidence intervals)*	*p Value*
	No	*Mean (SE)*	*No*	*Mean (SE)*		
Grip strength:						
Right hand	13	16·6 (0·8)	15	16·8 (1·2)	−0·2 (−3·2 to 2·8)	0·90
Left hand	13	15·9 (0·7)	15	15·9 (1·1)	0·0 (−2·0 to 2·0)	0·99
Bimanual accuracy:						
Beads	13	17·2 (1·3)	16	17·1 (1·3)	+0·1 (−3·5 to 3·7)	0·96
Unimanual accuracy:						
Pegs	13	25·4 (1·1)	16	24·6 (1·4)	+0·8 (−2·9 to 4·5)	0·66
Peg frame						
Right hand	13	13·0 (0·8)	16	14·3 (1·3)	−1·3 (−4·5 to 1·9)	0·41
Left hand	13	13·5 (0·9)	16	14·4 (1·2)	−0·9 (−3·9 to 2·1)	0·53
Cognitive task:						
PDCT	13	12·8 (2·1)	15	12·0 (2·0)	+0·8 (−5·0 to 6·6)	0·77
Height	13	135·1 (1·9)	16	135·1 (2·2)	0·0 (−5·9 to 5·9)	0·998

The differences between mean test results are positive or negative and the meaning of directional changes for each test is explained in the text.

performance taken was a significant difference between the two groups of children observed. In four measures (grip strength right hand, grip strength left hand, dots and number of taps right hand) the control group performed marginally better. In the remaining four measures (taps left hand, beads, screws, and pegs) the test group of children had higher scores.

Table 2 compares the scores achieved in 1982. On this occasion in addition to the motor indices, it was possible to compare also cognitive function as measured by the PDCT and height. None of the measures showed a significant difference between the two groups. The cognitive and all five tasks of motor skill marginally favoured the test group of children while the index of hand strength marginally favoured the control children.

Discussion

The fears that administering iodine during pregnancy may compromise fetal development as a consequence of maternal thyroid inhibition via the Wolff-Chaikoff effect may be allayed by the data presented here. The relatively small number of children in this study inevitably raises the possibility of a type II statistical error. Even this is unlikely, however, as most measures employed both in 1978 when the children were aged 11 and in 1982 when they were aged 15, favoured the test group more often than the controls. It is pertinent that the measures that most nearly approached significance were the bead threading and pegboard tests in 1978. These measures proved the most discriminating when applied to all the children in the trial reported previously.[9]

In the trial reported here 4 ml of iodinated oil were given to the test group of mothers during pregnancy whereas current World Health Organisation recommendations are for smaller amounts to be administered (1–2 ml),[3] thus further reducing the risk of thyroid inhibition. Furthermore, the Wolff-Chaikoff effect was demonstrated in iodine replete rats; that a similar inhibition of the thyroid gland follows iodine administration to an iodine deficient human population has not been demonstrated.

In contrast to the clear evidence that maternal iodine deficiency may severely compromise the development of the fetus, there is no evidence that the administration of iodine at recommended dose levels has any deleterious effect. Although it is necessary to keep a constant watch for any complication arising from the mass prophylaxis of iodine deficient populations, all the available evidence points to a highly advantageous benefit to risk ratio.

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Nasogastric feeding at home: acceptability and safety

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Abstract

A questionnaire was administered to 70 families with experience of home enteral nutrition. All but one patient received at least some of their feeding overnight. During 11 041 patient days of home enteral nutrition, no serious complications were seen. Sleep disturbance was common, however, and affected 59 parents and 35 children. A nocturnal cough or 'chestiness' were noted in 10 children suggesting occult gastro-oesophageal reflux. Enteral feeding disposables were not prescribable by general practitioners, and funding for the equipment was inadequate in the hospital and community. The mean time to arrange funding for equipment was eight months (range two weeks to two years). Parental views on home enteral nutrition were positive and none felt that its disadvantages outweighed the benefits. Altogether 35 children were described as being more happy and active. Given adequate preparation and continued support at home, parents can manage home enteral nutrition safely and effectively.

Increasingly, we are using enteral nutrition in children at home. This is related in part to an increased awareness of the prevalence of malnutrition among children admitted to hospital with chronic disease.[1–5] It is also a recognition of the potential benefits of nutritional support in children with chronic disorders such as Crohn's disease,[6] congenital heart disease,[7] malignancy,[8] cystic fibrosis,[9] renal disease,[10] and liver disease.[11] Recent case studies have supported the view that children receiving specialised nutritional support can be nursed effectively at home.[12–14] Although there is a large body of literature describing the practical techniques,[15 16] no study has examined the prevalence of complications associated with home enteral nutrition. We therefore undertook to investigate parents' and children's experiences of home enteral nutrition, focusing particularly on any practical difficulties encountered.

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Subjects and methods

SUBJECTS

Seventy consecutive families with experience of home enteral nutrition between January 1987 and April 1988 were identified from the records of the nutritional care team at the Children's Hospital. The indications for nutritional support comprised chronic renal failure (n=8), cardiac disease (n=8), cerebral palsy (n=2), malignancy (n=8), chronic liver disease (n=8), Crohn's disease (n=7), severe food intolerance (n=2), gastro-oesophageal reflux (n=10), short bowel syndrome (n=3), dysphagia (n=2), and failure to thrive attributable to an inadequate nutritional intake (n=12).

METHODS

Both parents from each family were questioned by one of us (CEH), either when attending the outpatient clinic or by telephone. The questionnaire was designed to record data about the type of equipment used, and also to explore parents' experiences of managing home enteral nutrition.

PATIENT PREPARATION AND PARENTAL TEACHING

Teaching programmes were tailored individually by the nutritional care sister. In general, however, training always included the safety aspects of enteral feeding, psychological preparation of the child, equipment maintenance, recognition of problems, and guidance on how to cope with them. Interpreters were used as necessary and teaching programmes extended where communication was more difficult. Play therapists helped to prepare the children psychologically for enteral feeding. For toddlers we used play techniques to focus on enteral feeding, and a range of treatment scenarios were prepared. Through play the child was asked about his or her memory of any previous admissions to hospital. We spent a great deal of time with parents, looking not only at the mechanics of enteral feeding but also at the psychological aspects. We gave parents reinforcement literature and toddlers were given a booklet called *Roo and Joe*, which describes the story of a child receiving nasogastric feeding. The booklet was specifically prepared by staff at the children's hospital and printed with financial support from Sherwood Medical.

Older children were prepared for nasogastric feeding by assessing their level of understanding and perception of their disorder. We explained to them why it was necessary to begin feeding. Time was spent looking at and handling enteral feeding equipment.

A photograph album and video was shown to them, which depicted previous patients passing their own nasogastric tubes. Diagrams in a booklet describing relevant anatomy associated with the digestive and respiratory tracts were discussed with them. They were told about the sensations encountered as the tube is passed and how they could learn to cope with them. They were also introduced to other children receiving or who had had enteral feeding.

PATIENT DISCHARGE

A joint decision was made by medical, nursing, and dietetic staff, and children were discharged when parents were considered competent and confident enough to look after enteral feeding. On discharge from hospital enteral feeding pumps were provided on temporary loan, and one month's supply of disposable equipment was given to parents.

The general practitioner was informed and appropriate district nurses and health visitors were contacted and given details of illness and the reasons for enteral feeding.

The child's parents were given one week's supply of the feed from hospital. The general practitioner was asked to prescribe the feed subsequently.

Results

The median age (range) at the start of home enteral nutrition was 3·5 years (6 weeks–15 years). A total of 11 041 days of home enteral nutrition were studied. Three types of enteral infusion pump were used: Viomedex (n=34), Kangaroo 330 (n=34), and Cow and Gate (n=2). Setting up the feeding system at night took a median (range) of five minutes (3–15).

SUPERVISION

In 59 families, each parent took joint responsibility for setting up the feed and looking after it overnight. In 11 families one parent took sole responsibility, usually the mother. Fifty nine parents got up in the night in order to check on their child and the accuracy of the pump, but in no case did any parent find it necessary to remain awake all night. No nasogastric tube fell out or became displaced into the respiratory tract and disconnection from the giving set was uncommon.

FEEDING REGIMEN

Forty six of the children received only overnight feeding, and 23 were fed both during day and night. The median (range) duration of feed infusion was 12 hours (4–24). One child with a tracheostomy received feeds only during the day.

NASOGASTRIC TUBES

Two types of tube was used. Fifty children had polyurethane Silk (Merck) tubes and 20 a polyvinylchloride (PVC) tube (Portex). Silk tubes were used when feeding was expected to last for longer than one month; they were changed monthly and required a guide wire for insertion. PVC tubes were used for short term feeding and were changed weekly as the tube becomes rigid if left longer.

Silk tubes were popular with parents and children because they were soft and easily inserted. However, 10 out of 50 parents using this tube reported that they blocked readily. This was usually prevented by flushing the tube with water after feeds.

Changing the Silk tube only once a month was seen as a clear advantage over PVC tubes. Five children who tended to vomit changed from a Silk to a PVC tube because they found that the more flexible Silk tube was more easily displaced by vomiting. Babies and toddlers often pulled their tubes out when first inserted, but after the first day tolerated them well. Thirty four parents were taught how to pass their child's tube.

The children were taught to pass their own tube at night, removing them in the morning. The median (range) age of these children was 8·75 years (5–15 years). In the remaining families, tubes were passed by hospital nurses, the nutritional care sister, or community nurses.

FAMILY SUPPORT

In general, parents were satisfied with the level of support offered to them. Parents were told to contact the nutritional care sister and dietetic staff at the hospital with any queries or problems. Sixty families commented that the support provided from the hospital was essential and they welcomed this reassurance. One in six children were visited by a paediatric district nurse who visited parents daily. All parents commented on the excellent care provided. Two thirds of the children under 5 years of age were seen by their health visitor. Six families had received help from a social worker since starting home enteral nutrition. Twenty families reported that community nurses without paediatric training knew very little about nutritional support for children, but in most cases provided helpful moral support. Sixty three families kept in regular telephone contact with members of the nutritional care team. We were able to obtain telephones through social services for families whose children were starting nasogastric feeding. All 20 families whose children were over 2 years of age who required feeding for longer than six months were successful in their application for an attendance allowance.

SUPPLIES

Disposable equipment for the feeding pumps was given to the parents for the first month at home. In general, there was no recognised budget in the community for disposable equipment and pumps for children at home. The Children's Hospital was therefore required to continue to supply equipment to 40 of the 70 families. When it did occur time taken to arrange funding was eight months. Twenty three of the families reported that the sheer weight of feeds caused a problem when carrying them home from the chemist. Eight families initially had problems getting feed from their chemist, as many feeds often required a special order. Dietetic staff often had to contact chemists to organise this. Eight general pratitioners would only give parents a prescription for one week at a time, a practice which they explained on the basis of the cost of the feeds.

SYMPTOMS RELATED TO HOME ENTERAL NUTRITION

After the introduction of nocturnal nasogastric feeding 35 children suffered from sleep disturbance: related to nocturia (n=20), vomiting (n=10), the need to defaecate (n=3), and abdominal pain (n=2).

Ten children developed a night time cough suggesting possible occult gastro-oesophageal reflux. However, in no cases were symptoms severe enough to warrant stopping feeds. Two children were further investigated and gastro-oesophageal reflux confirmed. One of these children was born with oesophageal atresia and tracheo-oesophageal fistula and had had a gastric interposition. She received enteral feeds via a nasojejunal tube, but continued to have reflux and have repeated chest infections; she subsequently had a feeding jejunostomy. The other child presented as an infant with laryngeal stenosis secondary to severe gastro-oesophageal reflux. At the age of 6 years he was started on nasogastric feeding and is awaiting a further antireflux procedure. In neither child was nasogastric feeding thought to have precipitated reflux.

BENEFITS OF HOME ENTERAL NUTRITION

Thirty four parents reported spontaneously that their child appeared more happy and active after the introduction of home enteral nutrition. A similar number spontaneously reported that home enteral nutrition gave them a new sense of freedom. This feeling was mainly the result of not having to devote so much time trying to get their child to eat.

The families with children with complex heart disease felt that home enteral nutrition had prolonged their child's life and enabled them to spend more time together. This comment was echoed by three families of children awaiting liver transplantation. Twenty eight families felt that home enteral nutrition had prevented admission to hospital and allowed care to be given at home.

The nutritional state measured at the start and end of home enteral nutrition demonstrated improvement in all patients in terms of weight for age centile, midarm circumference centile, and arm muscle area.

DISADVANTAGES OF HOME ENTERAL NUTRITION

In 36 children the nasogastric tube was the object of unwelcome public interest. Older children were selfconscious and inhibited about going out, and many reported teasing by their peers. This problem was prevented by teaching them to pass their own tube at night and to remove it in the morning.

Two schools were reluctant to allow children with nasogastric tubes to attend, but discussion with the nutritional care team resolved this problem. Thirty nine families reported that initially they were very distressed when their child's tube was passed. However, once in situ the children were not upset by the tube.

SERIOUS COMPLICATIONS

In 11 041 days of home enteral nutrition there were no instances of major complications such as aspiration, hypoglycaemia after interruption of feed, or entanglement in the tubing.

Discussion

Home enteral nutrition is used increasingly in the management of a wide variety of childhood disorders. Although we saw no serious complications, minor problems were common—for example, sleep disturbance affected 60 parents and 35 children. However, overnight feeding enabled the child and their family to lead a more normal daytime lifestyle.[17]

Our policy was to try and make feeding regimens flexible so that family routines were disrupted as little as possible. For example, one mother preferred to restrict feeds to the early evening as her child had a tracheostomy and required frequent tracheal suction overnight, which could provoke vomiting.

Enteral feeding pumps generally functioned well, but further development with regard to portability and alarm systems are still required.[18] The Viomedex pump has good alarm systems, but parents found it necessary to check the rate of infusion frequently when using this system.

The Kangaroo pump was well accepted by all parents, delivers feed in increments, and has an alarm system which indicates interruption in feed delivery. Unfortunately, the pump is not designed to be portable, but will run from an integral battery for a few hours.

The Cow and Gate pump was used by two patients. This pump is fitted with an alarm and is relatively portable, but unlike the other pumps, there is no carry pack available. Parents reported difficulty finding babysitters willing to cope with a feed pump. We now encourage other relatives and close friends to come to the hospital to be taught feeding techniques so that they can relieve parents from time to time. Silk tubes are routinely used for long term feeding and are well accepted, although the PVC tubes were less likely to become displaced by vomiting.

Ensuring adequate supplies of disposable equipment was often a problem. Such equipment is not available on prescription, and the nutritional care team is not funded to provide equipment for families in the community. Referring hospitals often ignored requests to supply equipment to parents.

It is now the policy of our hospital to write to the unit general managers in the community asking them to provide appropriate equipment. Unfortunately this request is sometimes refused on the grounds of lack of funding.

Parents had to order equipment well in advance from the community agencies and many continued to ask for hospital supplies because of irregular supplies sent. One family obtained disposable supplies directly from the chemist by special arrangement with the health authority.

Guidelines relating to funding and supply of equipment and disposables are urgently needed.[19] It is clearly an anomaly that general practitioners may prescribe feed products but not the equipment necessary for their administration.[20] In the meantime our findings confirm that home enteral nutrition can be managed both safely and effectively by parents, provided they are given adequate training and support.

We would like to thank all parents and children who contributed to this study.

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Cranial computed tomography in tuberculous meningitis
Thirty Californian children with tuberculous meningitis had cranial computed tomography and all showed hydrocephalus, which was said to be moderate or severe in 25 (Waecker and Connor, *The Pediatric Infectious Disease Journal* 1990;**9**:539–43). Twenty seven of the children had neurological signs, 10 with impaired consciousness. All were under 6 years old. Previous studies, which have included adults, have shown hydrocephalus to have a 70–100% sensitivity in the diagnosis of tuberculous meningitis. The specificity is unknown but obviously incomplete. I cannot share the authors' enthusiasm for computed tomography as a primary diagnostic procedure, but it would be useful to do it at some stage in the course of the disease and some children will need a shunt procedure.

ARCHIVIST

Methaemoglobinaemia after ingestion of amyl nitrite

R J Forsyth, A Moulden

Abstract

We report a case of methaemoglobinaemia in a 2 year old girl after ingestion of an 'aphrodisiac' containing nitrite. The availability of these products, their poor labelling, and their intended presence in domestic bedrooms all serve to increase the hazard they pose to young children.

Case report

A 2 year old girl was admitted deeply cyanosed. She was thought to have ingested about 5 ml of a substance identified by her mother as 'Liquid Gold' approximately one hour previously. The bottle was unlabelled.

On arrival she was pale, drowsy, hypotensive, and tachycardic and cyanosed despite facial oxygen. Peripheral vasodilation was evident over the bridge of the nose and the dorsum of the hands and feet. Her respiratory rate was 26/minute and air entry was unobstructed and adequate. Electrocardiographic monitoring indicated sinus rhythm at a rate of 130/minute.

The Poisons' Information Centre at Guy's Hospital advised that Liquid Gold might contain an organic nitrite.

Circulatory compromise was managed with intravenous plasma. Arterial blood gas analysis showed an oxygen tension of 35·3 kPa despite dark arterial blood and clinical cyanosis, and a diagnosis of methaemoglobinaemia was made. Intravenous methylene blue was given at a dose of 1 mg/kg. Ten minutes later, the patient was centrally pink. Her conscious state improved and she became normotensive with a pulse rate of 100/minute.

Subsequent analyses confirmed the poison to be amyl nitrite, and showed the methaemoglobin fraction of total haemoglobin on admission to be 0·43. Within three hours of arrival she was alert and orientated, and examination was normal. She was discharged home 24 hours after admission.

Discussion

Nitrites are widely used as aphrodisiac 'room odourisers' especially in the gay community,[1] and are sold under such names as Liquid Gold and Quicksilver.

Nitrites are absorbed transdermally and by inhalation and ingestion. The effects are vasodilation, penile erection, dilation of other smooth muscle including the anal sphincter, reflex tachycardia, increased cerebral perfusion, euphoria, and methaemoglobinaemia. In excess, cardiovascular collapse ensues.

Methaemoglobin is formed by the oxidation of the iron in haemoglobin [$HbFe^{2+}$] to the [$HbFe^{3+}$] state. The resulting molecule is unable to bind oxygen resulting in an impairment of oxygen delivery to the tissues. Erythrocytes reduce naturally occurring [$HbFe^{3+}$] both by NADH dependent mechanisms, which represent 95% of the total activity under normal conditions, and NADPH dependent mechanisms, for which methylene blue acts as a cofactor, permitting increased activity of these latter pathways.[2]

Clinically, methaemoglobinaemia usually follows exposure to drugs or chemicals, nitrites being the most commonly reported cause. Neonates have an increased susceptibility to acquired methaemoglobinaemia, due to decreased activity of methaemoglobin reductase enzymes. Methaemoglobinaemia had also been reported after exposure to topical nitrites in disinfectants and dietary *nitrates*, which are reduced to nitrites by intestinal flora. We are unaware of descriptions of this increased susceptibility persisting beyond infancy.[3]

The diagnosis may thus be suspected from a history of exposure to an oxidant substance, and by the demonstration of a surprisingly high arterial oxygen tension given the apparent degree of cyanosis. *Measured* oxygen saturation will be low, but the saturation figure given by most gas analysers, which is *calculated* from the measured arterial oxygen tension assuming a normal dissociation curve, will be high. Arterial blood remains blue even after exposure to oxygen.

Treatment comprises ventilatory and circulatory support with volume expansion and intravenous methylene blue. An initial dose of 1–2 mg/kg is diluted and given over five minutes. A therapeutic effect should be seen within an hour. Methaemoglobin fractions of over 0·3 are usually symptomatic; fractions over 0·7 are incompatible with life.

Although methaemoglobinaemia after exposure to nitrites is well recognised, the ready availability through sex shops and the like of compounds containing nitrites increases the importance of familiarity with this fact. Such sales are not subject to regulation under the Medicines Act as no therapeutic effects are explicitly claimed, although sale to minors is prohibited by the Intoxicating Substances Supply Act 1985. Samples we have seen do carry hazard warnings, and describe their contents as alkyl nitrites, but on a plastic wrapper that is destroyed in opening. The result is an unidentifiable bottle left open in a bedroom as an 'odouriser'. It can only be a matter of time before another such bottle is found by an inquisitive toddler.

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Bleeding from duodenal lymphangiectasia

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Abstract

An 8 year old girl with recurrent upper gastrointestinal bleeding was found to have localised duodenal lymphangiectasia by fibreoptic endoscopy. She did not show physical signs or laboratory evidence of significant enteric protein loss. A low fat diet seemed to prevent further bleeding. Duodenal lymphangiectasia may be associated with gastrointestinal bleeding in children.

Intestinal lymphangiectasia is a disease characterised by dilated lymphatic channels in the mucosa, submucosa, and serosa, as well as mesentery of the intestine.[1] This generalised disorder of lymphatics usually occurs in the small intestine and causes excessive intestinal protein loss.[1] The variant of intestinal lymphangiectasia in which blood, as well as protein, was lost in the bowel was described in two adult patients.[2 3]

We report a case of a girl with repeated upper gastrointestinal bleeding associated with duodenal lymphangiectasia without enteric protein loss.

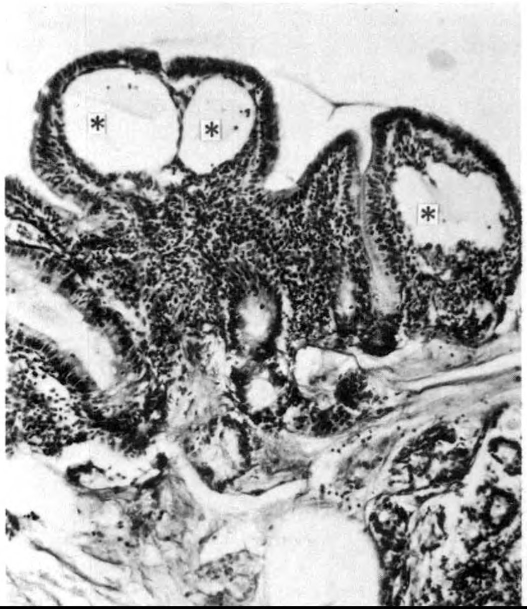
Case report

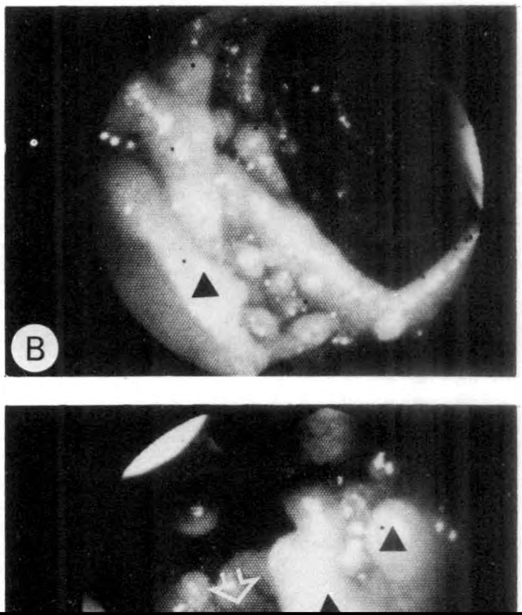
An 8 year old girl was referred for further investigation of her upper gastrointestinal bleeding. Two days before admission she experienced painless haematemesis and melaena. Her parents denied any kind of previous drug ingestion, nose bleeding, diarrhoea, vomiting, or retching.

On admission the clinical findings were normal. Her body weight was 27 kg and height 126 cm; these were both on the 50th centile.

Laboratory investigations showed a haemoglobin concentration of 90 g/l, and a leucocyte count of $9\cdot4\times10^9$/l with lymphocytes at $4\cdot5\times10^9$/l. Her erythrocyte sedimentation rate was 15 mm in the first hour. Urinalysis was normal. Total serum protein concentration was 58 g/l and albumin 36 g/l. Repeated stool examination for ova and protozoa was negative. Contrast radiography of the upper intestinal tract was normal. Abdominal technetium scanning was negative. ~~Ear, nose, and throat examination and~~ laryngotracheoscopy were negative.

After two days of fasting upper gastrointestinal endoscopy showed a normal oesophagus, stomach, and duodenal bulb. Descending duodenal mucosal folds were oedematous with





Mother and Child

[redacted]

numerous whitish elevations, each the size of a millet seed (figure B and C). Multiple mucosa biopsy specimens demonstrated intestinal lym-

[redacted]

diarrhoea and hypoproteinaemia.[1] The absence of fat in the diet prevents engorgement of the intestinal lymphatics with chyle, thus prevent-

Cardiac echinococcosis with fatal intracerebral embolism

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Abstract

A previously well 7 year old boy presented with sudden loss of consciousness and fitting. No evidence of trauma or space occupying lesion was identified. Death occurred the next day due to cerebral infarction caused by embolised fragments from a ruptured left ventricular hydatid cyst that was found at necropsy.

ful introduction of hydatid eradication programmes.[1] Increasing recognition by farmers of the danger of feeding offal to farm animals has been one factor in this reduction. In childhood most cases can be successfully surgically treated with fatal outcomes being unusual (5%).[1] The following case demonstrates, however, an extremely rare occurrence of sudden collapse with death due to cerebral infarction from embolised hydatid cyst fragments.

[redacted]

laminated hydatid cyst wall to both middle cerebral arteries (fig 2B) associated with early ischaemic changes in both cerebral hemispheres. A second hydatid cyst was present within the liver, which showed the characteristic external laminated cuticula, internal germinative membrane, and hydatid sand. Death was attributed to acute cerebral infarction due to bilateral middle cerebral artery hydatid embolism from a ruptured hydatid cyst of the left ventricle.

Discussion

Hydatid disease in children is unusual and the most commonly affected organs are the liver and the lungs.[1 2] Although it occurs predominantly in sheep raising countries the disease is world wide in distribution.[3] Cysts may remain asymptomatic for a number of years and presenting symptoms and signs, such as abdominal discomfort, jaundice, and biliary colic, are related to the mechanical effects of growth and compression of adjacent parenchyma and ducts.[3]

The normal life cycle of the echinococcal cestode involves passage between definitive carnivore hosts, such as the dog, with transmission of eggs that have been shed in faeces to intermediate hosts such as sheep, cattle, or pigs.[1] Infection of humans with the tapeworm is, therefore, not part of the normal cycle and is usually caused by inadvertent contamination with eggs from infected dogs.

Cardiac involvement by echinococcus at all ages is rare and has a reported incidence of around 0·5% to 2% of cases in the literature with the left ventricle being the most common site of cyst formation.[4] In children the incidence appears more variable with no cases being found in a 35 year review of 114 cases of hydatid disease at the Royal Children's Hospital, Melbourne, Australia,[1] compared with two cases (4·4%) in a 20 year series of 45 patients from the American University of Beirut Hospital, Lebanon.[2] Involvement of the heart occurs when bloodborne embryos disseminate from the liver through the pulmonary vessels to lodge in tissues supplied by the coronary arteries.[4]

It is felt that contraction of the heart provides a natural resistance to the maintenance of viable hydatid cysts, thus accounting for the lower number of intracardiac cases.[5] Unfortunately, however, this feature may also result in spontaneous rupture of a developing cyst once it has reached a certain size. This has led to cases of sudden death occurring, the underlying mechanism of which is felt to be anaphylaxis.[4]

It is uncertain whether the reported patient's fall in the playground ruptured the intracardiac cyst, or whether this occurred spontaneously. Hydatid embolism from the heart is, however, a rare sequel that usually occurs in adults when portions of a ruptured hydatid cyst travel from either the right side of the heart to the lungs, or from the left side to the brain or periphery.[5 6] Unexpected death in childhood due to this complication in a previously undiagnosed patient is exceptionally rare.

This case is reported to draw attention to the possibility of sudden (<24 hours) embolic death in childhood due to previously undiagnosed hydatid disease. Although echinococcosis is not a major health problem in most Western countries, isolated cases continue to occur. Certainly, increasing migration and travel to endemic areas will contribute to its continued occurrence. For this reason it is important to be aware of the early manifestations of hydatid disease, particularly given the potential for a fatal outcome at a relatively young age.

We would like to acknowledge Dr JM Brown who performed the necropsy in this case.

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CONTROVERSY

Effect of the new GP contract on child health clinics

T D van Zwanenberg

[redacted]

place within general practice. Sadly their approach is half hearted and both activities remain as optional extras. Fortunately most practices were already engaged in both, and more are beginning to get involved. Furthermore, there is comfort in the experience of community based antenatal and postnatal care, which used to be provided in clinics and which is now virtually exclusively provided within general practice.

Why is the government's intention quite proper? Why should preschool child health surveillance and immunisation take place within general practice? Why are clinics inappropriate?

As long ago as 1976 the Court report concluded that the tripartite structure of child health services between general practice, hospitals, and community clinics was undesirable.[8] The Court committee's first recommendation stated that 'the organisational structure of the child health service should be changed to provide an integrated 2-tier system based on comprehensive primary care linked with supporting consultant and hospital care'. With the Alma Ata Declaration two years later the World Health Organisation (WHO) acknowledged that the only way to achieve their global goal of 'health for all by the year 2000' was through the development in each country of a system of primary health care, providing comprehensive curative and preventive care accessible at the point of first contact with the national health system.[9]

Britain was fortunate among nations in having a primary health care service based on general practice already in existence. The development of multidisciplinary primary health care teams (PHCTs) had been expressed government policy since 1974.[10] It is no surprise that Jarman and Cumberlege concluded that primary health care in this country is best provided by a PHCT of GPs, community nurses, and others working together from good premises serving the population registered with the practice.[11]

It is simply historical accident and the antithesis of comprehensive primary health care that preventive child care should have been provided and administered as a separate vertical system.

Much of the debate about child health surveillance has been concerned with its content and quality, rather than where and by whom it should be carried out. A survey in 1983 revealed that each of 192 health districts in England ran its own wholly different child health surveillance programme.[12] The choice seemed to depend more on the whim of the individuals responsible than on any apparent rationale such as research. Yet high quality surveillance programmes can only be developed if research becomes an obligation. By 1985 the WHO had admitted that preschool screening had not been adequately evaluated.[13]

The Hall report has made a useful contribution to the debate about content and usefulness,[14] though even its conclusions have been disputed by some.[15] Any discussion about quality is meaningless without adequate measures of process and outcome. It is the responsibility of the health professionals concerned to define a basic screening programme with an appropriate reporting system for both interventions and outcomes to allow evaluation. This is beginning to be achieved in some parts of the country,[16] but we are a long way from being able to demonstrate that examination of babies at 6 weeks of age leads to a reduction in the later presentation of congenital dislocated hips or undescended testes.

In short, anxieties about the quality of surveillance provided by PHCTs[17] need to be addressed by the establishment of a properly evaluated reporting system and appropriate training for GPs and health visitors and not by continuing a similarly unproved parallel service.

Preschool child health surveillance and immunisation as an integral part of comprehensive primary health care provided by PHCTs based on general practice has much to recommend it. The GPs have continuing clinical responsibility for the child and its family in sickness and in health. The families are in regular contact with the team, and most mothers receive antenatal care and family planning advice from the team. The GPs and health visitors regularly attend to other matters during well baby clinics, for example social problems, intercurrent family illness, family planning, and postnatal care. This is convenient for families. Further the GPs are best placed to catch children opportunistically—typically the most needy—when they fail to attend structured clinics. Better communication within the PHCT can overcome the problems of inconsistent and conflicting advice so many mothers receive.[18]

It has been suggested that the traditional medical officer of health responsibility for the health of the population should be undertaken by GPs,[19] each practice being responsible for individual and group health surveillance in its own registered population. The potential of the defined GP list is now beginning to be realised as practices rapidly computerise and increasingly accept responsibility for anticipatory care.

Eventually practices will report annually on the health status of the practice population,[5] and GPs may stand as powerful medical advocates of behalf of their patients. The PHCTs using their accumulated and up to date computerised information could make a significant impact on the planning and delivery of services. In short, a vision of the future has emerged in which PHCTs will have the critical roles of identifying need and providing essential health services for their defined population. This vision must include the children.

In contrast what can community clinics offer? The buildings are mostly poorly designed, unattractive, and underused. They are staffed almost exclusively by part time clinical medical officers (CMOs) who have neither clinical responsibility nor adequate career structure. The appointment of consultant community paediatricians, while easing the pangs of guilt felt by their hospital colleagues, has done little to improve the lot of the CMOs. In many parts of the country the clinics are staffed by GPs working on a sessional basis or by junior medical staff.

The clinics do offer certain positive benefits. The doctors have a special interest (and most have had special training) in preventive child care. They dispense vitamins and cheap baby milk. Most provide a sociable clinic atmosphere. All of these features are steadily being reproduced within general practice. In particular there is no reason why milk and vitamins have to be provided exclusively from clinics. Furthermore the claim that clinics are geographically more accessible is unsupported by the evidence. GP premises are more numerous and more widely distributed in the community.

The question now is not whether general practice can or should provide primary preventive care for children, but how quickly it can be done.[20] If some GPs are unable or unwilling to provide the service, CMOs could be invited to carry out these tasks with access to the practice records and premises. Such a move would foster integration, and might provide better career opportunities for CMOs.[21]

This will allow consultant community paediatricians to concentrate on supporting PHCTs with advice, training, and suitable reporting systems, while accepting responsibility for school health services and the community based services for children with special needs. The clinics, which are at best an expensive anachronism dispensing milk, vitamins, and condoms, and at worst a source of conflicting advice and wasteful duplication, could then be sold—probably to GPs who would upgrade them attractively as they have done so successfully with their own premises! It may be sensible to retain a few clinics to provide secondary paediatric care for those children who are better assessed and treated in a community setting, for example cases of child abuse.

For too long the clinics have been maintained on the grounds that GPs are not ready. It is time we placed our resources and faith in comprehensive primary health care based on general practice. This is essential for the future of our children.

I am indebted to Mrs Linda Redpath who prepared the manuscript.

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Child health clinics

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In the last two years one of the major arguments in the National Health Service has been for a reduction in the duplication of services. District health authorities which are euphemistically 'a little short on cash' look towards reducing their services and transferring the cost to another agency, often with the lame excuse that this agency can 'do it better'.

Who makes those decisions about the quality of the service and on what criteria? What may be perceived as 'duplication' by managers and doctors may similarly be viewed as 'choice' by patients or community health councils. There is usually a tendency in such circumstances for professionals to assume that they know what is best for users, often without asking. It is important, therefore, to scotch the myth held by some general practitioners (GPs) that the Court report recommendations said that they are the mainstay of child health surveillance.[1] In my view there are three key participants in ensuring good child health surveillance, these being the parent(s), health visitors, and doctors.[2]

I cited the issue of choice as one of the key elements of the argument in favour of child health clinics. Why do users of child health services prefer clinics run by the district health authority? On a visit to a local clinic I asked a mother why she brought her child to this clinic rather than taking her baby to her local GP run child health clinic. The answer was simple and direct 'You go to the doctor when you're sick, my bairn's not sick'. Clinics in Newcastle are linked to the notion of health. If GPs are to succeed in providing clinics capable of matching those provided by the district health authority they must become more adept at giving patients information about their services and in involving them as equal partners in health care.

In most child health clinics patients appear to be much more involved and engaged. The clinics meet other health needs not merely connected with sickness. Brighton Community Health Council commented in a report in 1984 'At almost all clinics in the Brighton Health District parents are able to purchase baby milk and vitamins following advice from the health visitor'.[3] Contrast the following descriptions of child health clinics 'Perhaps the ideal clinic is exemplified by Conway Court in Hove. This is a purpose built clinic . . . . There are two voluntary helpers in addition to the paid staff . . . . able to offer development checks as well as immunisation. The clinic is open at other times during the week for health education, cytology clinics, stroke clubs, parentcraft classes, post-natal support groups and the screening of school age children'[3] with the following comments from a staff study day in Newcastle: 'consumers' feel like 'people' at child health clinics and part of the general population. At GP clinics it is very much medical and illness orientated. Consumers suddenly act out the 'patient' role when surrounded by telephones ringing, receptionists bleeping doctors, and doling out repeat prescriptions to unsteady elderly patients who haphazardly negotiate the worn out toys scattered around the waiting room (study morning for community doctors, Newcastle upon Tyne, March 1990). I have no doubt this is a slightly cynical view but it is significant that it came from a group of health care professionals rather than users of the service.

Parents and children prefer to attend child health clinics because of the wider variety of services that are offered. None of these services appear to be more highly favoured alone than any of the others, for example the provision of welfare foods and milk.[4] The combination of space to park expensive buggies, the provision of health information, and peer support, however, seem to make child health clinics a preferred option.

One of the major reasons that is given to community health councils for retaining a clinic is its accessibility to mothers and babies from the local community. In most studies the majority of mothers choose to walk to the clinic. A survey by Aylesbury Vale Community Health Council showed that 66% of the clinic attenders surveyed lived less than a mile from the clinic and 51% of them walked to the clinic. One in three of the mothers brought at least one or more children with them.[5] The same trend appeared in responses to questions to clinic users in Newcastle, which seems to represent a degree of correlation between clinics in both rural and urban settings. Mothers that we spoke to in a clinic in Fenham in Newcastle said that they preferred to go to their local clinic. A number of mothers had moved into Fenham from other parts of the city and had swapped child health clinics but had not changed their GP to one in a closer location to their new home. The problem is exacerbated by the fact that some GPs in Newcastle refuse to agree to practice boundaries for their patients. Mothers also cited the timing of the clinic and the lack of an appointment system as being preferable to them than those provided by local GPs. The fact that the clinic ran in the early part of the afternoon meant that mothers could prepare food, take their child to the clinic, and then collect an older child from school. The fact that the clinic worked efficiently meant that mothers liked the 'drop in' style and could allocate enough time for a visit. Many commented that their GPs could not provide such a service due to the pressures of overrunning surgeries, emergencies, and so on or else the GP had instituted an appointment system which meant that both parents and doctors felt obliged to abide by time constraints on appointments. The effect of this on users was highlighted in a recent survey by *Which?* magazine that said that 89% of patients felt that doctors should spend more time listening to patients.[6]

The question also has to be asked about the equitable distribution of child health services across a city or health authority area. It is quite obvious that the level of need in terms of health or sickness will vary. Could all users in a city like Newcastle expect the same quality of service for their children from GPs wherever they live? I recognise that there are a large number of extremely dedicated and hard working GPs located in inner city areas providing an excellent service, but the rules controlling access to their lists means that they often become victims of their own success as mothers and children rush to join their practice. What choice and quality is there for those who are not lucky enough to gain access to such care? The potential for not finding and intervening in health risks in children in areas of high health deprivation is appalling. As independent contractors some GPs seem to hold a different view of the delivery of necessary health care. In Newcastle the community health council recently agreed to the closure of an inadequate building that was being used for a child health clinic on the proviso that the same clinic would be reprovided in a local GP's surgery with superior premises adjacent to an area with a number of young families. Some members of the local medical committee have questioned the desirability of this, presumably in case it unfairly draws attenders to the GP's list for other services. Such concern over competition that improves the delivery of health services can only be to the detriment of patients. The nature of the contract between the GP and the family health service authority/family practitioner committee (FHSA/FPC) make it difficult for any outside body, such as the community health council or community groups, to apply pressure to ensure needs are met. The situation becomes a little easier in dealing with the district health authority provision where decisions have to be discussed and consulted upon and where users have a variety of mechanisms at their disposal to ensure that they are heard.

One of the concerns that only a few parents have dared to mention is the relationship between GPs and patients in cases of suspected child abuse. The situation is fraught with dangers for the child, GP, and both parents. What happens to the doctor/patient relationship when the 'family doctor' suspects that abuse is taking place. How skilled are all GPs at detection? I would suggest that parents who suspect that their child is being abused may prefer their suspicions allayed or confirmed by an 'external specialist' whom they can trust. Such cases are likely to be extreme but they do highlight the issue of the skills that clinic staff have that are built up by specialisation and experience. A number of professionals have concerns over the ability of GPs to provide an effective service that is of a high quality. A number of commentators have pointed out that large scale surveillance by GPs may be a waste of time in view of their workload, which GPs remind us is increasing with the new contract. Some have gone even further in terms of commenting on the quality of service that is offered.[7] 'The statement in the Royal College of General Practitioner's report that "we have no doubt that from the point of view of children the immediate start of a comprehensive system of regular child examination through general practice across the country as a whole can be provided by general practitioners trained as they are now"[8] is one which has to be questioned.'[7]

Further evidence of the GPs lack of skills were highlighted in a survey in the Northern region. Only 52% of the GPs surveyed had done a six month residential paediatric job and only 9% had the diploma in child health. As if these figures were not disconcerting enough in terms of expertise, only 27% had done a residential paediatric refresher course in the last five years.[9] Such figures should be disturbing to health care professionals, but how are lay people to obtain such information and then make an informed choice about the most effective provider of screening facilities for their child?

There must also be concern over the ability of parents to seek redress in the event of a mistake being made in assessing their child's health. Community health councils have long held the view that an effective complaints mechanism is a useful quality assurance tool to ensure that patients' needs are met and that the service can be improved. The present GP/FHSA/FPC system means that a GPs clinical judgment cannot be questioned, by a patient, except perhaps through the informal complaints procedure. The importance of an effective complaint system can only be endorsed from the following response of a GP. 'The message of the course was to listen to parents and never dismiss their fears. Aileen Tyler, mother of a growth retarded child, who was ignored by her GP for years, had us all squirming in our seats'.[10] The GP and FHSA/FPC complaint system does not compare with the district health authority complaint's procedure on clinical issues where second opinions can be sought and full investigations undertaken into the type of care given, even amounting to a review by consultants from outside the region. Such a safeguard is a reassurance to parents and children alike. There are also issues such as the premises being open to inspection and scrutiny by the community health council, which is not an option for GP provided services. Some GPs are wary of user involvement in record keeping with patient held notes and so on. Only a few GPs provide such services, which are often provided as a matter of course in the district health authority clinics.

Finally, there is the matter of the staff who support doctors in providing child health clinics. Health visitors provide much of the care in both types of clinics but those based in child health clinics can draw on support from a wide range of colleagues and professions. I would add hastily that this is not to denigrate the work done by health visitors in primary health care teams, but not all GPs seem to be able to collaborate either equitably nor as well as they suspect with the health visitors in their practice.[9] Nor do all GPs collaborate well with other agencies. It is worth bearing in mind that the Black report listed accidents and poverty as the two main determinants of childhood morbidity and mortality.[11] Where clinics integrate into communities it provides a better focus for an intersectorial problem solving approach to improve the chances of better child health system. The ability of GPs to meet all the requirements of their new contract and to maintain a high quality of service in all areas of service delivery is open to question and has been highlighted by GPs themselves. The last thing that users want is a reduction in choice where a service is foisted onto them which is in the interests of GPs' salaries rather than patient needs.

Clinics provide better services for child health services because they have the potential to be an integral part of the communities they serve and can develop a health rather than illness orientation. The staff and volunteers working in them are often local people who can pass on and respond to local information much more effectively than the majority of GPs. Clinics have space and time to treat parents and children as people rather than patients and perhaps most importantly of all, clinics can draw on extra resources, both cash and staff, in a flexible way to meet changes in need as long as they are run by the health authority. In terms of consumer preference clinics seem to have advantages that make the GP alternatives pale in comparison.

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CURRENT TOPIC

European paediatrics—unity with diversity?

T L Chambers

The 900 consultant paediatricians in Britain might occasionally pause to reflect that they have about 30 000 paediatrician colleagues within the European Community (EC). The total number in greater Europe between Lisbon and the Urals must approach six figures. The geographic and political map of the continent has radically changed during the last year and it is likely that colleagues working in the wider Europe will wish to develop links with British paediatricians and these will involve education and medical practice. However measured the national political approach to association and integration the professional pressure is likely to be strong—and British paediatricians should welcome it.

1992/3

Nothing apocalyptic is likely to happen on 1 January 1993 as free movement of doctors within the EC already exists. The Single European Act merely commits the EC to establish a single market by the end of 1992. However the dominant influence of the market may challenge some UK practices such as the limiting of patient access to specialists by insisting on referral from primary care. The defence of free consumer choice is becoming an imperative and this could have enormous organisational and financial consequences, not only for those doctors practising in countries where they are remunerated by item of service payments. European Council directives in 1975 laid down the rules for member states for mutual recognition of qualifying degrees and diplomas both for undergraduates and postgraduates and in general practice harmonisation of training is almost complete. Trainee doctors from the EC are classified in the UK for medical manpower purposes as career doctors and a steadily increasing number of juniors from the continent are occupying training posts in paediatrics in the UK. Many have already tasted medical life as undergraduates on elective secondments and some British universities are participating in the Erasmus scheme of undergraduate exchange with mutual recognition of specialty courses, and a similar scheme (TEMPUS) has been established with some Eastern European countries. So why do more European paediatricians not apply for posts here, especially as unemployment is a familiar feature of medical life in some European countries? The answers are not known but likely barriers are language, earnings, and differences in practice—not to mention the climate. Of course there has traditionally been close exchange of doctors at all levels between the UK and the Republic of Ireland.

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Clinical practice

We recognise great differences in our professional practice and customs throughout Europe. The most striking is that very many continental paediatricians are primary care physicians for children rather than specialists such as in the UK, the Republic of Ireland, the Netherlands, and Denmark. There are other profound differences in approach exemplified by the different attitudes of the medical professional bodies in Britain and the Netherlands towards euthanasia. While wishing to draw together as a professional group whose main interest is the child, many paediatricians will want to preserve aspects of national medical life. The challenge facing those of us holding office in European paediatric representative bodies is to reconcile the apparently conflicting impulses for integration and individuality.

Education

With such diversity in medical practice there will be many educational routes to the end of being recognised as a paediatrician. However there is a strong case for harmonising some aspects of training in the EC countries because of the free movement of doctors. The Confederation of European Specialists in Paediatrics (CESP) (see below) has recently approved a document on paediatric training in the EC for submission to the governing bodies of European medicine. The requirements for training paediatric specialists (such as those in the UK) reflect our current practice. The European junior doctors feel that our approach is too *laissez-faire* and that the doctors should be insisting on higher standards of education and a more professional approach to postgraduate training, particularly the earmarking of time for education, rather than accepting the passive osmotic approach to learning that is traditional in the UK.[1] The Association for Paediatric Education in Europe has done much to improve quality in undergraduate and postgraduate training in paediatrics in Europe and the recent report of the Padua group is a welcome stimulus.[2]

Research

Many examples of international collaboration exist and the European Society for Paediatric Research is a major forum for academic exchange. Similarly the various European paediatric specialty societies (nephrology, gastroenterology, and nutrition, etc) regularly hold scientific meetings attended by paediatricians from East and West Europe and further afield. Recently the successful British Paediatric Surveillance Unit (BPSU) scheme has been presented to Europe (there is already collaboration between two European countries: the UK and Republic of Ireland) and thanks to the combined enthusiasm of Professor David Baum, Chairman of the BPSU Executive Committee and Professor Schmidt, the Secretary General of the Union of National European Paediatric Societies and Associations (UNEPSA) it is hoped to develop a model of European paediatric surveillance, opening up immensely challenging opportunities for collaboration in research and clinical practice.

Administration and politics

There are two non-academic European paediatric bodies: UNEPSA and CESP.

UNEPSA

This is a body whose constituents are the many national paediatric associations throughout the continent of Europe. Its governing body is the general assembly of Presidents and Honorary Secretaries of the member associations and it meets in alternate years, usually linked to a scientific programme. The next meeting is in Berlin in 1992. An executive committee meets two to three times between general assemblies to conduct UNEPSA business. There is a journal *Paediatrics in Europe,* which is distributed to paediatric chair holders throughout Europe. UNEPSA has formal links with WHO Europe and the International Paediatric Association.

CESP

This is the paediatric monospeciality group of the European Union of Specialists (UEMS), which reports to bodies which are eventually answerable to the European Commission. Hence views of paediatricians may be incorporated into European parliamentary legislation. Its members are two delegates nominated by the national paediatric societies of the EC member states there are now observers from non-EC countries, particularly those that may apply for EC membership. The CESP meets annually and its President, Secretary General, and Treasurer conduct business between meetings. The CESP has a responsibility for harmonisation of paediatric medical services and practice and has produced a document on harmonisation of immunisation in Europe* and is looking into neonatal biochemical screening. Its activities in paediatric education have been referred to previously. With the recent European changes it is likely that membership of the CESP will enlarge. This will make its constitution resemble that of UNEPSA, a working party of which has recently suggested that the two bodies discuss means of integrating their work and avoiding duplication and possible conflict of advice to governments and the wider medical profession.*

Links with the British Paediatric Association (BPA)

A past President of UNEPSA, Professor Angel Ballabriga (Spain) is an honorary member and its current Secretary General, Professor Eberhard Schmidt (Federal Republic of Germany) was recently elected an overseas member. I was recently fortunate to succeed Professor Jean Rey (France) as UNEPSA President. He had done much within the union to promote its thinking towards the millenium. Dr David Harvey is the past president of the CESP, Dr Georges Van Den Berghe (Belgium) and Dr Jean-Claude Schaak (Luxembourg) are BPA overseas members and former CESP Presidents. Dr Schaak is currently its energetic Secretary General. Professor Gavin Arneil and Dr Tony Jackson have played a distinguished part in the development of European and international paediatrics.

The future

The health and medical care of European children pose many challenges to medicine and it is encouraging that British paediatricians and the BPA are confronting them with enthusiasm and energy. Many will have reservations about the idea of a 'Eurochild' and 'Europaediatrician' as lacking the individuality that is the spice of clinical practice. Perhaps we should be thinking about the British or Portuguese or Hungarian child and paediatrician working to common European goals in clinical practice and medical education through a variety of national means, thus promoting unity through diversity. Windy Eurorhetoric? I do not intend it to be so.

1 Permanent working group of European junior hospital doctors. Policy statement on postgraduate medical education. *Med Educ* 1989;23:339–47.
2 Organising committee for the workshop on postgraduate paediatric training in Europe—Padua 1989. Postgraduate training in Europe for the next decade. *Arch Dis Child* 1990;65:644–5.

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*Copies available from the British Paediatric Association, 5 St Andrew's Place, London NW1 4LB.

Archives of Disease in Childhood 1991; 66: 164–168

CURRENT PROBLEM

Cognitive deficits in children treated for leukaemia

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Psychological effects of chronic childhood diseases

In common with children who have other chronic diseases, those with leukaemia experience a great many restrictions and disadvantages; school life is inevitably interrupted, and many children miss several months schooling immediately after diagnosis.[1 2] All children are regularly absent during the course of their treatment either for routine hospital appointments, because of minor infections, or because of outbreaks of contagious diseases—such as measles or chickenpox—among the other children.

Such interruptions can have adverse consequences both for their academic achievements and for social relationships. Continued absences mean that the children miss essential lessons, and are continuously behind in written work. Circles of friends may regroup and exclude ill children, who may also return to school changed people, both in appearance and in character. A feeling of isolation can reduce the children's sense of belonging to the school and their participation in activities.

Other factors, too, work against chronically sick children in the classroom. Teachers are poorly informed about the implications of disease and may feel reticent about having to teach such children. Many fail to understand the nature of medical complications, and worry that they will be unable to deal with medical emergencies should they arise. A great deal has also been written about the extent to which teachers have reduced expectations about how far chronically sick children should participate in all school activities, or perform academically. These dilemmas have been noted particularly among teachers of children with asthma[3] and diabetes,[4] as well as among teachers generally.[5] Teachers also tend to rate children with cancers as less sociable and more isolated and withdrawn than their healthy peers.[6]

Parents, too, may communicate to sick children that school attendance and academic achievement are less important after the diagnosis of a chronic condition. Many parents report that such diagnoses force them to put their various ideas into perspective, and acknowledge the importance of less materialistic and competitive ideals.[7]

Children with chronic diseases typically experience some restrictions of activities, especially in terms of mobility or participation in sports activities. This applies no less to those with leukaemia.

Given these restrictions and disadvantages, it should not be surprising that children with chronic diseases commonly show deficits in intellectual achievements,[8 9 10] and in behavioural and social functioning.[11] Certain 'risk' factors—especially social disadvantage or the occurrence of other medical complications, as well as the characteristics of the disease itself (such as the extent to which it is associated with visible deficits or reduces the child's mobility)—seem to aggravate the possibility of adverse psychological repercussions.[12 13]

For those with leukaemia there is the additional 'risk factor' of their treatment regimens. Both radiotherapy and chemotherapy have been implicated as potential sources of damage to the developing central nervous system. Sometime after the introduction of this treatment protocol parents began to report difficulties for their children at school.[14] Typically, poor performance was noted especially in mathematics, problem solving, attention, and concentration skills.

Moss and Nannis argued that central nervous system prophylaxis may be particularly damaging for young children, as compensatory mechanisms are less likely to operate when radiation treatment includes the whole brain.[15] They hypothesised that greater intellectual impairment would also occur in younger children who received radiation treatment before the brain was fully developed (below 5 years). Deficits could be expected to become more noticeable with time. This hypothesis is based on the assumption that new learning is more affected than previously acquired skills, and that generalised damage early in life has a profound effect on the individual child.

Given parental reports of underachievement, and the possibility of radiation induced damage to the central nervous system, a considerable amount of research has been generated concerned with the short term and long term effects of treatment for leukaemia on the intelligence quotients (IQ) and academic achievements of children with the disease.

I will now consider how adequately this research has been designed and carried out, what conclusions can be drawn, and what implications may be drawn for the education of these children.

Problems in study design

To put the research findings into perspective, I will first consider the problems in study design that are encountered in work of this kind.

First of all, it is impossible to show conclusively that any deficits in intelligence or behaviour that are observed are directly attributable to radiotherapy, chemotherapy, or any other disadvantages of the disease experienced by the child and family. For ethical reasons it is impossible to conduct the controlled experiments that would be necessary to reach such conclusions. With few exceptions, researchers have failed to acknowledge the interdependence of these factors.

Secondly, there has been an over-reliance on IQ scores as the outcome measure. IQ scores are themselves subject to considerable variability (as a function of the child's motivation or the testing style of the examiner). They are unlikely to be sufficiently sensitive to monitor fluctuations or gradual declines in ability, and they are not valid indicators of the child's ability outside the traditional classroom setting.

Thirdly, there has always been the vexed question of the suitability of different 'control' groups. The result has been that children's scores may be compared with standardised norms, scores of 'healthy' children (matched for age, gender, and social class), healthy siblings, or children with other chronic or acute conditions. Though all of these comparisons have some merits, none are likely to yield a definitive answer.

Fourthly, researchers have for convenience opted for 'cross sectional' designs. More rarely, longitudinal studies have been conducted. Though the longitudinal method is essential to understand the processes by which deficits may occur, many difficulties arise concerning patient attrition and repeated testing. In addition, specific aspects of treatment may change depending on the child's progress. For all these reasons, longitudinal studies have not always yielded findings that are as clearcut as might have been hoped.

Review of published reports

A report by Soni *et al* showed no differences in IQ scores between children treated for leukaemia by irradiation of the central nervous system, either in comparison with a 'control' group of patients treated without irradiation, or with a group of patients with solid tumours.[16] The number of children taking part was small, however, and there was a five year difference in the mean age of those with leukaemia treated by irradiation of the central nervous system and the control group with solid tumours. These findings were replicated in other studies.[17 20]

A substantial number of reports, however, did suggest that children treated by irradiation of the central nervous system, or methotrexate, or both, did show IQ deficits compared with both healthy controls and with children with other cancers who were not treated in this way. The question became therefore not whether irradiation of the central nervous system was associated with deficits at all, but rather which children or skills were most vulnerable.

Gender

One of the most consistent findings to emerge was that cognitive impairment after irradiation was more common and more severe in girls than in boys.[21 22] Waber *et al*, for example, found that 89% of girls and 54% of boys showed some learning impairment measured by a conglomerate index of IQ and academic achievement.[22] Though this was consistent with the related finding of more impairment of growth in girls,[22 23] the results were not borne out by other work that indicated that there was greater vulnerability among boys.[24] Waber *et al* proposed a two stage model to account for these findings.[25] One set of processes were hypothesised to affect all children treated by irradiation of the central nervous system and tended to increase the incidence of cognitive dysfunction and learning disorders. The second was developmentally determined and affected only girls, with the result that boys showed impairment in discrete skills, and girls showed more generalised impairment.

Age at diagnosis

Perhaps one of the most important inferences was that children who were younger (especially under 3 years old) were more vulnerable than children who began treatment later.[21 26–30] These studies were often based on samples of children still undergoing treatment or who had only recently completed treatment, and seemed to support the hypothesis put forward by Moss and Nannis that younger children would be more vulnerable.[15] This might also be predicted from understanding changes in the social or emotional impact of the disease depending on the child's age.[31] Other work concerned with long term survivors has, however, not confirmed the hypothesis of continual declines in performance after treatment.[32]

Specific compared with generalised deficits

Although a number of studies suggested that irradiation of the central nervous system resulted in a mild generalised loss in ability,[33] a number of other studies pointed to discrete losses in specific skills. For example, it was noted that particular deficits occurred in quantitative, memory, and motor skills, especially for those treated by irradiation before they were 5 years old.[26]

The possibility that there were specific cognitive deficits has been noted by others.[19 21] Deficits were noted particularly in mathematical skills, attention, concentration, and memory. It is not clear why this should be so. It may be that mathematical skills are easier to measure than linguistic or creative skills, or that differences in the way that children are taught makes it more difficult for the child to make up for absences in mathematics. It is possible that the deficits in mathematical skills have been overemphasised. In this respect, it should be noted that Peckham *et al* reported that the range of deficits shown in their sample was wide and therefore the repercussions of radiation were determined in part by individual and genetic factors, in addition to the treatments.[34]

Integration of results

Cousens *et al* attempted to put some order into this area by conducting a meta-analysis of all research published between 1975 and 1985.[35]

Of these 30 studies, 17 were included in the meta-analysis, as only these fulfilled the criteria of having patients with acute lymphatic leukaemia who were treated with cranial irradiation as subjects and a control group in which irradiation was not used, and of providing enough statistical information for a full scale 'IQ effect size' to be calculated. The effect size was calculated from the difference between the mean scores of the control and treatment groups divided by the standard deviation of the control group scores. In addition, 10 variables were coded wherever possible, including the number of patients and controls, mean age at testing for patients and controls, age at diagnosis or irradiation for patients, number of units of radiation given, duration of treatment, time since treatment, type of control group, and IQ measuring instrument used.

The mean overall effect size was −0·72, equivalent to an IQ deficit of about 11 points. Three variables correlated significantly with the effect size ($p<0·05$): (i) the age of the patients at the time of diagnosis (showing greater decrements the younger the patients were diagnosed); (ii) the age at testing of the controls (again showing greater decrements the younger they were at the time of testing); and (iii) the control group (greater decrements being found when healthy controls were compared with control groups who had other types of cancer).

The association between effect size and length of time since end of treatment was not significant, though greater decrements were associated with longer lapses of time since the completion of treatment. There were no associations between effect size and size of the sample or control groups, age at testing of patients, length of treatment, instrument used to measure IQ, or specific control group.

Subsequent analyses were conducted on two separate groups of studies, those in which patients were under 5 years of age at the time of irradiation, and an older group. The younger group ($n=12$) had a mean effect size of −0·82 compared with the older group ($n=11$) with a mean effect size of −0·53.

From this analysis, Cousens *et al* concluded that patients receiving prophylactic treatment including irradiation of the central nervous system showed a decrease in full scale IQ score (in the order of 11 points).[35] In addition, children treated at younger ages showed greater deficits. They calculated a mean loss of 17 points for children treated before 4 years of age, compared with 7 points for those treated later. They also suggest that IQ scores do not drop to their lowest levels until some time after treatment. Greater decrements were observed in studies in which children had been treated at least three years earlier ($n=18$) compared with those treated more recently ($n=5$).

Although the meta-analysis was excellent in the way in which it drew together much of the published work and indicated the mean decrement in IQ, it is an inappropriate technique for studying other issues. For example, it is still not clear whether patients have a generalised deficit in IQ, or whether specific skills are affected, nor is it clear whether IQ decrements are continuous and progressive, nor if there is a point at which scores stabilise, and even some recovery occurs. We know relatively little about the effects of irradiation as a function of gender, or social class, yet both these may be critical mediators of decrements.

Long term survivors

Most of the work reviewed so far has been based on patients who were treated for leukaemia and survived without recurrence over relatively short periods of time (up to five years). As the numbers of patients who survive even longer has increased, interest has slowly shifted towards the consequences for those patients. Research concerned with long term survivors is of interest for two reasons. Firstly, it is necessary to establish whether children who are well, and have completed treatment, show the same kind of deficits as those who are in shorter term remission. This is relevant to the practical question of whether these children continue to need remedial help at a time when they are considered to be medically 'cured'. Secondly, the study of long term survivors is relevant to the issue of how irradiation of the central nervous system affects development; the issue is whether children's abilities are permanently blunted, or if and when intellectual recovery occurs.

Malpas suggested that achievements at school leaving age (in terms of examination passes) compared favourably with those of the rest of the population.[36] Subtle deficits in long term survivors have, however, been identified by Mulhern *et al* and Peckham *et al.*[32] [34]

Peckham *et al* studied 23 children who had been treated by irradiation of the central nervous system and intrathecal methotrexate 8–10 years earlier.[34] Lower than expected scores were obtained in both reading and mathematics after consideration of scores before treatment and currently. Difficulties were noted particularly in attention and concentration, memory, sequencing, and comprehension. They argued that long term survivors showed specific deficits rather than generalised retardation. Despite this some children seemed to achieve appreciably more than expected, presumably reflecting the fact that individual or remedial help and parental support could do much to alleviate the potential damage of treatment of the leukaemia.

In a comparable study, Mulhern *et al* studied 183 children all of whom had been treated for cancer at least five years earlier and were currently free of disease.[32] Problems with both academic work and adjustment were found among children who were older on beginning treatment, who had been treated by irradiation of the central nervous system, and who lived in one parent families. Both these studies pointed to the continuing need to support and offer remedial help to long term survivors. Inevitably, however, children in this kind of study were treated some time ago, and therefore may have received different—perhaps less acceptable—treatment compared with today's standards.

Interventions and implications

Most studies concluded that children with leukaemia treated by irradiation of the central nervous system should be offered additional educational help at school. Mulhern *et al*, for example, suggested that deficits could be identified in long term survivors indicating that remedial help may be advisable throughout treatment and for many years after.[32]

We have, however, made little progress in determining the kind of remedial help that may be most beneficial. Though additional individual help with basic skills may alleviate the worst side effects of irradiation, real progress in modifying specific deficits can be achieved only by the development of programmes aimed directly at the particular cognitive deficits that children experience. There are consistent indications that concentration and attention skills, or problem solving abilities, are most likely to be affected. Remedial help needs to be concentrated on developing these skills, rather than relying on methods to help healthy children with more general learning difficulties.

It is also naive to assume that academic achievement is determined solely (or even predominantly) by educational interventions. Children's achievements in school are also dependent on intrapersonal factors such as self esteem and coping skills, as well as position within the peer group. We know that children with leukaemia can experience lowered self esteem and can be subject to teasing from peers.[35] In a study of 138 long term survivors who had completed treatment, Greenberg *et al* found that, although most children scored within normal limits on measures on self-concept, depression, and locus of control, a proportion showed significantly lower scores.[37] Those with residual deficits had poorer self concept, more depressive symptoms, and a more external locus of control compared with those with mild deficits or none at all. In the final analysis, however, perhaps we need to examine the fundamental question we are asking. Research has focused on identifying 'cognitive deficits' in children treated by irradiation of the central nervous system, and while acknowledging the difficulties inherent in such an approach, most workers have nevertheless made the assumption that somehow radiation effects would outweigh any disadvantages to the social or emotional experiences of the family. There are, however, many reports that suggest that the children themselves may suffer adverse emotional consequences and depression,[38] and that families undergo enormous upheaval and stress.[39 40] Even healthy siblings can be adversely affected.[41] The treatment that is currently offered to children with leukaemia may ultimately be shown to be associated with some iatrogenic effects, but for the moment these are not proved. It is possible and highly desirable, however, that in the meantime interventions are directed at those consequences of treatment that are more easily identifiable. Routine liaisons with schools and teaching personnel should be offered, and psychological support (in addition to practical or financial help) provided for all family members who need it.

For children themselves interventions may need to foster intrapersonal and interpersonal skills in addition to focusing on academic abilities. Children with leukaemia may need to explain their disease, its treatment, and implications to others, and can experience considerable unease in doing so. These difficulties are of course shared by children with other chronic diseases. For example, those with diabetes may need to explain why they need injections, or why they may need to eat before physical activities. There is evidence that children with diabetes[42–44] and asthma[45] can benefit from training in 'social skills', which may help them resolve and deal with difficult social encounters. It may well be that these approaches need to be integrated with more straightforward educational interventions if we are really going to help children with leukaemia to be thoroughly integrated and competitive with their peers.

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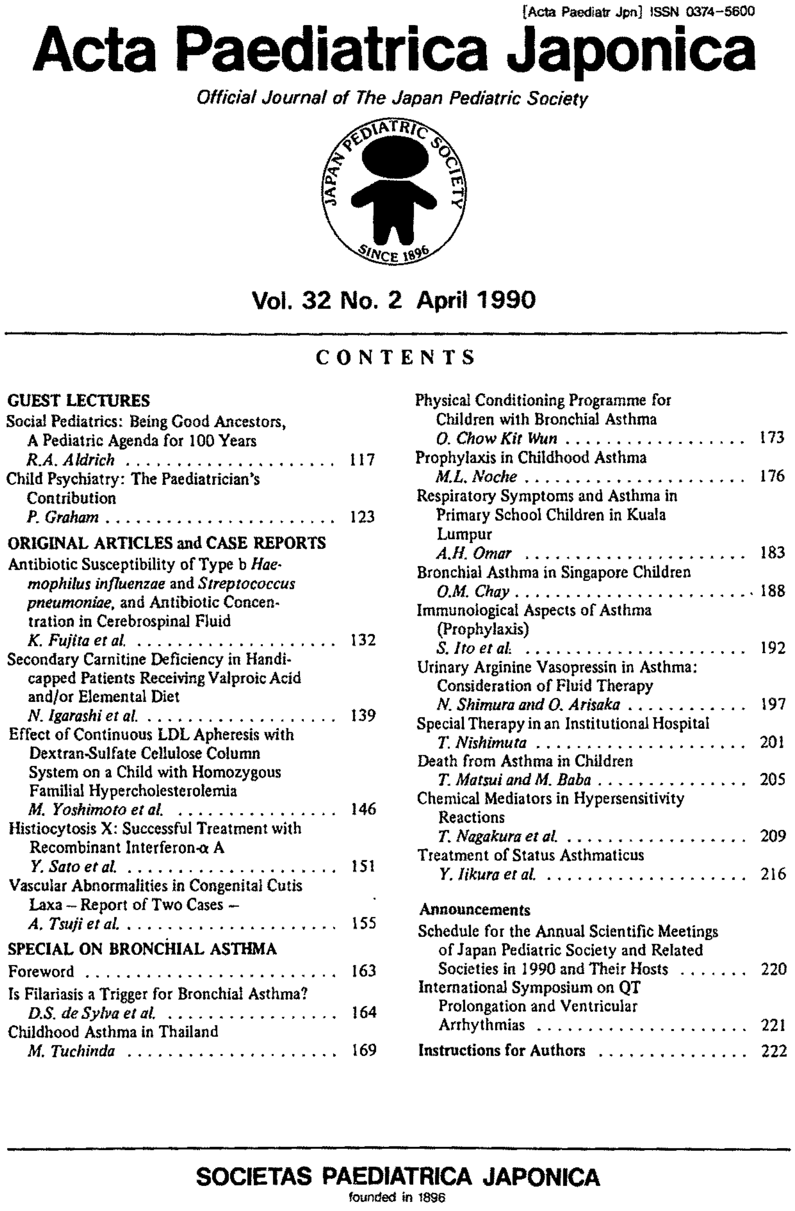
SISTER JOURNALS—JAPAN



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SOCIETAS PAEDIATRICA JAPONICA
founded in 1896

Acta Paediatrica Japonica 1990.

Acta Paediatrica Japonica

The Japan Pediatric Society was founded in 1896 and the society's journal *Acta Paediatrica Japonica* is now in its 32nd volume. Each issue has a size and layout very similar to the 'old style' *Archives of Disease in Childhood.* Six issues are produced each year, and comprise between 110 and 120 pages. The October 1989 issue contained 11 original articles, six case reports, and announcements of forthcoming paediatric meetings. This issue is fairly typical of style for the journal. The standard of the original articles is extremely good, and make the readers aware of the wide range of Asian medical problems and their prevalance.

There are guest lectures published from a range of international experts and, for example, in the April 1990 issue Philip Graham, Professor of Psychiatry at the Institute of Child Health in London has produced an excellent lecture entitled 'Child Psychiatry: the Paediatrician's Contribution'.

In that same issue is a report of the 6th Asian Congress of Pediatrics Satellite Symposium on bronchial asthma. Views on asthma from Sri Lanka, Thailand, Hong Kong, the Phillippines, Malaysia, and Singapore as well as six articles from a variety of Japanese units give a range of views of the topic from the role of filariasis in bronchial asthma to the minutiae of chemical mediators in hypersensitivity reactions. A topic of major importance in Asia is hepatitis B virus infections and is described as the 'common enemy of Asia' in another satellite symposium published in the December 1989 issue of the journal. In the December 1989 issue there are short communications on mass screening for neuroblastoma, cerebrospinal fluid neurotransmitters of the newborn with neonatal asphyxia, and the effect of recombinant hepatitis B vaccine in low response children. Kawasaki disease is only one of the eponymous Japanese syndromes reported in the *Acta Paediatrica Japonica* and it is increasingly important to be aware of the disease states of Asia and to be able to recognise the same disorder or similar disorders in our own communities. As well as recognising the similarities there are interesting differences highlighted in the Japanese journal with regard to the incidence of inherited metabolic disorders.

Every university with a paediatric unit should have this leading paediatric journal available and heads of paediatric departments should be prepared to beg, borrow, or 'acquire' the 6000 yen (£22·00) for each year's subscription.

FORRESTER COCKBURN

LETTERS TO THE EDITOR

Antibiotic treatment of suspected neonatal meningitis

SIR,—The editorial by Drs Gandy and Rennie on antibiotic treatment of suspected neonatal meningitis has provided a timely review of an important neonatal problem.[1] We were surprised to see the use of intraventricular aminoglycosides being advocated for the treatment of Gram negative meningitis, as there is now considerable evidence to suggest that intraventricular treatment is not only ineffective, but may, in addition, be hazardous. We were further disappointed to read the authors' rebuttal of the important arguments made by Drs Short[2] and Tarlow[3] in their subsequent letters to the editor.

The argument put forward by Gandy and Rennie rests on the observation that the aminoglycosides do not penetrate well into the cerebrospinal fluid, and adequate cerebrospinal fluid concentrations to treat Gram negative bacillary meningitis are not achieved when aminoglycosides are administered intravenously. In the past, intrathecal aminoglycosides seemed a logical form of treatment. Since the introduction of the third generation cephalosporins, however, the position has changed. These agents are highly active against *Escherichia coli* and other coliforms, and when administered intravenously, achieved cerebrospinal fluid concentrations several times the minimal inhibitory concentration for these organisms.[4] It is therefore difficult to justify the use of intraventricular treatment.

The authors seem unconvinced by two multicentre trials of intrathecal aminoglycosides in neonatal meningitis.[5] Not only was no benefit derived from aminoglycosides given by either the lumbar or the intraventricular route, but the mortality was higher in the patients receiving intraventricular treatment. The authors also avoid the worrying evidence that suggests that the administration of intraventricular aminoglycosides results in higher cerebrospinal fluid concentrations of endotoxin and cytokines than seen after systemic treatment alone.[6] In view of the increasing evidence that bacterial toxins and host inflammatory mediators are responsible for the damage to the central nervous system associated with bacterial meningitis,[3] treatment that increases cerebrospinal fluid concentrations of these substances should be avoided.

The arguments that have developed subsequent to the annotation on the antibiotic treatment of suspected neonatal meningitis highlight the different philosophical approaches to what makes good paediatric practice. We believe that practice should be guided by the results of published therapeutic trials rather than personal belief. As the only trials to date have demonstrated a poorer outcome in patients receiving intraventricular aminoglycosides, this form of treatment should not be advocated.

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1 Gandy G, Rennie J. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65:1–2.
2 Short A. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65: 810.
3 Tarlow MJ. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65: 810.
4 Kaplan SL. Recent advances in bacterial meningitis. *Advances in Pediatric Infectious Diseases* 1989;4:83–110.
5 McCracken GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram negative bacillary meningitis of infancy. *Lancet* 1980;i:787–91.
6 Mustafa MM, Mertsola J, Ramilo P, Saez-Llorens X, Risser RC, McCracken GH. Increased endotoxin and interleukin-1-beta concentrations in cerebrospinal fluid of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. *J Infect Dis* 1989;160:891–5.

Drs Gandy and Rennie comment:

The correspondence generated by our editorial has highlighted the difficulties experienced by those attempting to manage this condition. We endorse the use of cefotaxime but, as stated in the original annotation, the published results with this agent contain only small numbers of babies (less than 50) and there has not been the improvement in mortality or morbidity which was expected. This could be because of the frequency of ventricular enlargement in neonatal cases which may require drainage or make the cerebrospinal fluid minimal inhibitory concentration inadequate, and it is for these babies and for those who fail to respond to systemic treatment alone that we continue to recommend consideration of intraventricular treatment. The use of intraventricular reservoirs will naturally decline if cephalosporins have the success which is predicted for them.

Drs Heyderman and Levin are correct in their assumption that we remain unconvinced by results regarding 20 neonates with *Escherichia coli* meningitis contained in the only study using intraventricular treatment which was carried out before the introduction of cephalosporins, ultrasound, or intraventricular reservoirs.[1] We agree that ones clinical practice should be guided by the results of well conducted therapeutic trials of adequate size but for neonatal Gram negative meningitis we consider that such studies are yet to be published, and urgently need to be planned.

1 McCracken GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram negative bacillary meningitis of infancy. *Lancet* 1980;i:787–91.

Categories of preventable unexpected infant deaths

SIR,—As members of the Avon Infant Mortality Study Group we were surprised and disturbed by the recent paper from Sheffield by Taylor and Emery.[1] They came to the conclusion that in 43% of sudden unexpected infant deaths there was 'treatable disease' and, by implication, these deaths could have been prevented by appropriate health care intervention. This finding is at variance with our own observations.[2] We were also concerned to read that eight of 115 (7%) deaths in the Sheffield study were attributed to filicide, a finding which is at variance with our own experience of only one case of proved filicide in over 200 sudden unexpected death victims during a seven year period in Avon.

We see the parents of all infants who die unexpectedly in Avon within 72 hours of the death (most of them within 24) with the general practitioner and health visitor and collect detailed information from the parents, primary health care team, and hospitals. This contact includes a 'death scene' examination and a structured questionnaire on medical and social history.[2] All infants undergo a detailed standardised postmortem examination by a paediatric pathologist or a pathologist with special expertise in this field.[3]

For the past three years all sudden unexpected deaths of infants in Avon have been the subject of a formal multidisciplinary confidential discussion involving two pathologists, a microbiologist, a biochemist, an epidemiologist, and three paediatricians with extensive experience of infant care.

We have drawn up a classification of death using microbiological, gross pathological, and histological criteria. The results of the 95 infant deaths included in the first two years of our study (May 1987 to April 1989) are given below.

In seven (8%) of the total deaths we were able to identify a sufficient explanation for the death, while in 39 (41%) we identified evidence of a potentially significant illness at the time of death, but insufficient to account for the death. In the remaining 49 (51%) no significant abnormalities were identified. None of these deaths was thought to be due to filicide. These results are similar to those previously published by Arneil *et al* in the Scottish National Study.[4]

Taylor and Emery state that minor nonlethal defects may lower the threshold for the onset of severe illness and thus contribute to death. We are not aware of any evidence to support this contention. Signs of illness in infancy are very common,[2] and interpretation of their significance as contributory factors in infants who die requires carefully matched controls, which are lacking in the Sheffield study.

Workers in the field of sudden unexpected death in infancy have a great responsibility to the children of this country and to the parents of children who have died suddenly and unexpectedly. The paper by Taylor and Emery raises many questions about the interpretation of clinical, psychosocial, and pathological findings after the death of an infant but contains insufficient data to allow the reader to assess the validity of their conclusions.

We are well aware of the confidential nature of inquiries that have to be made where filicide is considered to be a possibility, but we call upon the authors of this work to make available the information that they have for confidential re-examination by an independent group of paediatricians and pathologists. The outcome of this fresh inquiry could then be submitted for publication in this journal.

These questions are too important to be left open by the lack of data in the paper by Taylor and Emery.

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1 Taylor EM, Emery JL. Categories of preventable unexpected infant deaths. *Arch Dis Child* 1990;65:535–9.

2 Gilbert RE, Fleming PJ, Azaz Y, Rudd PT. Signs of illness preceding sudden unexpected deaths in infants. *BMJ* 1990;**300**:1237–9.

3 Wigglesworth JS, Keeling JW, Rushton DI, Berry PJ. Pathological investigations in cases of sudden infant death. *J Clin Pathol* 1987;**40**: 1481–3.

4 Arneil GC, Gibson AAM, McIntosh H, Brooke H, Harvie A, Patrick WJA. National post-perinatal infant mortality and cot death study, Scotland 1981–82. *Lancet* 1985;i:740–3.

Drs Taylor and Emery comment:

The main differences between the Bristol and Sheffield views on unexpected infant death are firstly, that the Bristol group do not accept the concept that several contributory factors may result in a lethal situation, and secondly that they are unable to accept that filicide is the probable cause of a small percentage of cot deaths.

Our view is that many unexpected infant deaths are due to a combination of factors in the sense that but for the presence of all of these factors death might not have occurred.[1] The concept of contributory factors is one which is generally accepted—for example, the increased severity of infections in children who also have nutritional deficiencies or reduced pulmonary reserve due to residual lesions in the lung after perinatal damage. Dr Fleming and his group have themselves postulated that overheating and overwrapping may be a contributory factor in some cot deaths.[2]

The confidential inquiries undertaken by Dr Fleming and his group with case conferences being hospital based and hospital orientated are very similar to those undertaken in Sheffield in the 1970s, and their results are very similar to our own at that time.

In 1979 we started to hold our case discussions on all 'non-hospital' deaths in the family doctor's surgery. These case discussions are held when data collection, including a home visit by a doctor not concerned with the paediatric care of the family, is complete and the results of a full paediatric necropsy are available and at a time when the initial emotional impact of the death is lessening and more dispassionate views may prevail. These discussions, at which the general practitioner and health visitor are invariably present, are as much concerned with planning for the future health care of the family and of any subsequent child as with the cause of the baby's death. It is these confidential discussions with the general practitioner and health visitor that have revolutionised our views on the aetiology of unexpected infant death and have shown us the importance of family and background factors, and it is at these discussions that the possibility of filicide is occasionally raised. Deaths are only placed in this category if at the conclusion of the case discussion it is a unanimous decision that this was the *most probable* mechanism of death. The prime reason for identifying this small group (less than 10%) is so that an appropriate level of care—paediatric, psychiatric, and health visiting—can be provided for the family. Although the identification of possible filicide only forms a relatively small part of our inquiries, the denial of the possibility of this mechanism of death would also deny some families the extra care that they need.

Fleming *et al* state that our data should be 'inspected by an independent group of paediatricians and pathologists'. As we collect more than 50 pages of data after each death this would be a major undertaking. However, we have no secrets other than the confidentiality of information relating to individual families and would welcome a visit from Dr Fleming or one of his colleagues to look at our records, discuss our methods, and attend a case discussion.

1 Emery JL. A way of looking at the causes of crib death. In: Tyson Tildon J, Roeder LM, Steinschneider A, eds. *Sudden infant death syndrome.* London: Academic Press, 1983:123–32.

2 Fleming PJ, Gilbert R, Azaz Y, *et al.* Interaction between bedding and sleeping position in the sudden infant death syndrome: a population based case-control study. *BMJ* 1990;**301**:85–9.

Effective bronchodilator treatment by a simple spacer device for wheezy premature infants

SIR,—Yuksel and colleagues describe a cheap and easy solution to a common and difficult problem.[1] One cannot help but be impressed by the size of the improvement seen during active treatment.

There are, however, certain aspects of the study which concern me. Firstly, the study was not randomised and all the children were given active treatment after placebo. Although this is disputed by the authors, in this group of children where symptoms are likely to have been exacerbated by viral infections, one would have expected some improvement with time, irrespective of treatment. This possibility is borne out to some extent, as on active treatment there was a 27% reduction in the score for 'runny nose/unwell'; these are symptoms which are suggestive of a viral infection. These symptoms could not have been expected to respond to a bronchodilator and therefore should not have been added to cough and wheeze (their table 1). Also adding together scores for cough and wheeze (their table 1) could double the score for a single event. Admittedly the percentage fall in each symptom category, with active treatment, is remarkable.

Secondly, the authors state 'Administration of the bronchodilator resulted in an increase in functional residual capacity both immediately and during the two week active period'. This is patently not borne out by the results in their table 3, where there is no significant difference in functional residual capacity before and after terbutaline using a paired *t* test (mean (SD) before and after terbutaline: 252 (75) and 269 (58) in the placebo period and 322 (83) and 325 (95) in the active period). Indeed two and three subjects, respectively, showed a 'clinically significant' decrease in functional residual capacity after terbutaline compared with four and two with a 'clinically significant' increase. If we are to believe, as the authors suggest, that an increase in functional residual capacity reflects an improvement in lung function, then the long term improvement in functional residual capacity on active treatment occurred without any evidence of an immediate response. The authors do not address this discrepancy between the long and the short term benefit but misleadingly suggest that an immediate increase in functional residual capacity had occurred.

One is left with a sneaking suspicion that at least part of the improvement on active treatment, in symptoms and lung function, could be related to changes with time. Before accepting the alternative conclusion, that in this group of children twice daily terbutaline has a dramatic effect on symptoms, which is largely independent of its immediate bronchodilator properties, it would be wise to confirm the results with a better designed study.

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1 Yuksel B, Greenough A, Maconochie I. Effective bronchodilator treatment by a simple spacer device for wheezy premature infants. *Arch Dis Child* 1990;65:782–5.

Drs Greenough and Yuksel comment:

We thank Dr Wilson for her interest in our paper. In that preliminary study, as no previous data was available, we set out to assess if bronchodilator given by a simple spacer had any effect on symptomatic preterm infants in the first year of life. We found over the two week period in which bronchodilator was administered a significant improvement in lung function and reduction in symptom score.

We are surprised Dr Wilson felt it necessary to reanalyse the acute lung function data as we did *not* claim that the change in functional residual capacity 10 minutes after terbutaline was significant. We recognised and stressed in our discussion that the results could in part be explained by an improvement in symptoms with time and felt our results should be confirmed in a randomised trial—which, as a consequence we have subsequently completed (unpublished observations). In a randomised placebo controlled trial inhaled ipratropium bromide administered via a coffee cup, resulted in similar improvements in functional residual capacity and a reduction in symptom score. Unfortunately many infants are symptomatic in the first year of life, the coffee cup technique is cheap and easy; we therefore, like Dr Wilson, are impressed and we are also pleased with the size of improvement seen during active treatment.[1]

Gender and the progression of *Escherichia coli* 0157:H7 enteritis to haemolytic uraemic syndrome

SIR,—The epidemiologic studies of Milford *et al* continue to advance our understanding of Verocytotoxin producing *Escherichia coli* and the associated haemolytic uraemic syndrome.[1] Notable among their findings is the excess of females in the probable prototypic haemolytic uraemic syndrome subgroup and the observation that such excess has been observed previously in other studies. Our own studies have also previously suggested an excess of females among patients with *E coli* 0157:H7 associated haemolytic uraemic syndrome.[2] Although in a univariate analysis this excess was not significantly different from a control group of patients who suffered from *E coli* 0157:H7 enteritis only, a multivariate analysis disclosed that female gender was possibly an important predictor variable for progression to haemolytic uraemic syndrome.

In order to determine whether the latter association was coincidental, we continued our study to include 37 patients with haemolytic uraemic syndrome and 95 patients with only enteritis. The sex ratios (M/F) in the two groups were 17/20 and 53/42 respectively. In univariate analysis, gender was not associated with progression to haemolytic uraemic syndrome ($p=0 \cdot 414$), and gender was not a significant predictor variable in multivariate analysis. Our studies do not, however, include an analysis of the effect of gender upon the severity of haemolytic uraemic syndrome.

Although the potential for young age and prolonged use of antimotility agents to enhance the progression of *E coli* 0157:H7 enteritis to haemolytic uraemic syndrome might be explained on the basis of a toxin per body weight relationship, the designation of female gender as a risk factor might lead to alternate views on disease pathogenesis—for example, a gender difference for toxin receptors. Therefore, future studies should critically evaluate gender in the context of appropriate control groups.

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1 Milford DV, Taylor CM, Guttridge B, Hall SM, Rowe B, Kleanthous H. Haemolytic uraemic syndromes in the British Isles 1985–8: association with Verocytotoxin producing Escherichia coli. Part 1: clinical and epidemiological aspects. *Arch Dis Child* 1990;65:716–21.
2 Cimolai N, Carter JE, Morrison BJ, Anderson JD, Risk factors for the progression of Escherichia coli 0157:H7 enteritis to hemolytic-uremic syndrome. *J Pediatr* 1990;**116**:589–92.

Ready, steady, hiss

Sir,—Working in a Cambodian refugee camp reminded me how important both definitions and cultural influences are in timing developmental landmarks. In Britain control of micturition implies that the child recognises his full bladder and communicates this to the carer, a process attained by the majority at 1·5 years.

In the camp where there are no nappies and infancy is spent attached by a large sheet to the mother's side, however, mothers have developed a technique for toileting their infants at an earlier age that prevents themselves being wet all day, and may have unknowingly shone new light on the mechanisms of toileting. When she suspects that her infant's bladder is full, the mother hisses in his ear as she holds him in a squat position over the earthen floor. By between 6 and 12 months of age this hiss initiates prompt bladder emptying.

Little is known of the psychological basis for toileting, but if these observations are correct, then at least here classical (pavlovian) conditioning may have a role, in which the conditioned stimulus is the hiss, the unconditioned stimulus is the full bladder, and the response is the bladder emptying. At first sight this technique is reminiscent of the toileting history of B F Skinner,[1] the great proponent of operant conditioning in behaviour theory, who was successfully toileted by 9 months on a potty chair that played 'The Blue Danube' when she produced! Such music may be considered pleasant to the infant and, therefore, supportive of operant conditioning because it provides an incentive to urinate appropriately. The case for my description being of classical conditioning rests on the hiss of the mother being a neutral stimulus that is neither an incentive nor a deterrent to the infant in urinating (as neutral as the bells were to Pavlov's dogs).

I see no reason why this technique should not be studied further, and if found to be effective, may greatly help mothers involved in the exhaustion of nappy changing, regardless of which school of psychology this phenomenon supports.

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1 Skinner BF *The shaping of a behaviourist.* New York: Knopf, 1979.

Terminology in community child health

Sir,—Dr Stone's annotation on terminology in community child health was a useful airing of an important issue.[1] By and large, the definitions he proposes are clear and acceptable.

I have two points to make. Firstly, the definition of surveillance he proposed concerns a limited and a relatively small proportion of the work currently carried out by child health doctors and general practitioners in child health clinics. In many ways, restricting the definition of surveillance to cover the 'collection . . . and interpretation of indices of child health, growth, and development' is useful as it is near to the accepted lay definition of surveillance. However it should be made clear that this is different to the activity known as child health surveillance as described in the Court report[2] and more recently in the Hall report.[3] The latter consists of a more wide ranging activity, the emphasis of which is on the promotion of health and development with the implied active participation of parents in the process. The inappropriateness of the word 'surveillance', in terms of its connotations, for this activity were commented on in the Hall report but no suitable alternative was suggested.

The second point concerns Stone's patronising view of community paediatrics as a rather cosy, anachronistic, and insular specialty which, he states, feels uncomfortable at being neither in the main stream of hospital paediatrics or public health. I would refute this suggestion strongly. The Court report recommended a consultant led community child health service, of the sort that is currently emerging, as the best hope for improving standards of child health to all sections of the population. The working practices in community child health that have evolved since then are positive, effective, and in many cases, novel approaches to the problems of improving and integrating health services for children. That controversy exists, even surrounding terminology, is a measure of the innovatory nature of much of community paediatrics. Rather than seeing community child health 'trapped in a professional and organisational vacuum' I would see it as a model for other health services such as geriatrics, psychiatry, and even perhaps obstetrics, which still remain hospital and medically orientated despite the problems often being community related.

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1 Stone D. Terminology in community child health—an urgent need for consensus. *Arch Dis Child* 1990;65:817–8.
2 Report of the Committee on Child Health Services. *Fit for the future.* London: HMSO, 1976. (Court report.)
3 Hall DMB, ed. *Health for all children. A programme for child health surveillance.* Oxford: Oxford University Press, 1989.

Use of peripheral vessels for exchange transfusion

Sir,—I would like to congratulate Fok *et al* for reminding us again in a documented way that there is no need for exchange transfusions to be carried out 'the conventional way'.[1]

For the past six to seven years we have also used peripheral vessels for exchange transfusions as the preferred route particularly in ill preterm infants, and I would entirely concur with the authors' comments and conclusions. I would like to recommend a modification of their technique, however, which requires only one operator/observer, an important advantage in a busy neonatal unit. Two syringe pumps are required. The first is used to deliver blood through the peripheral vein. The second is modified and its action is reversed (that is, it pulls the syringe plunger) and is used to withdraw blood through the peripheral artery at the same rate chosen for the former. If such a modification is impossible then the operator withdraws blood through the artery at precisely the rate of the syringe pump. By using two syringe pumps, however, the movement of the plunger is more even and smoother and the likelihood of extravasation of blood and arterial spasm is minimised. There is only one potential hazard. The temptation to move away from the baby and let 'the system run on its own.'

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1 Fok TF, So LY, Leung KW, Wong W, Feng CS, Tsang SS. Use of peripheral vessels for exchange transfusion. *Arch Dis Child* 1990;65: 676–8.

Reflux vomiting

Sir,—In his comprehensive review of reflux vomiting Dr P J Milla suggests that the prone head raised position is the most effective therapeutic position and cites references to support this.[1] Yet in the first direct comparison of the prone flat and prone head raised (30 degrees) positions it has been shown that the flat position is just as effective.[2] This is an important practical observation. In the past, by a variety of methods, much effort has been spent maintaining infants in the raised position which we now know to be unnecessary. This is good news for both nurses and parents!

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1 Milla PJ. Reflux vomiting. *Arch Dis Child* 1990;65:996–9.
2 Orenstein SR. Prone positioning in infant gastro-oesophageal reflux: is elevation of the head worth the trouble? *J Pediatr* 1990;**117**:184–7.

Archives of Disease in Childhood 1991; **66**: 173–174

BOOK REVIEWS

Handbook of Immunological Investigations in Children. By J Graham Watson, A Graham Bird. (Pp 264; £25·00 paperback.) Butterworth Scientific Ltd, 1990. ISBN 0–7236–0973–X.

It is a problem in a rapidly advancing field such as immunology that for fear of being controversial or out of date authors fail to set down aspects of new research which are of great potential relevance to clinical practice for the benefit of practitioners. It is therefore not only timely but also courageous that two specialists should set down their personal clinical practice in a format designed to be accessible to the clinician with broader interests than immunology alone.

The book is a pocket sized manual which opens with a resume of basic immunology and the investigation of primary immunodeficiency, then covers the immunological aspects of investigation of diseases of each of the major organ systems in a series of 11 concise chapters and concludes with a very useful summary chapter of the major laboratory immunological investigations in clinical use, complete with paediatric normal ranges and types of specimen required. It is well referenced throughout to major easily accessible sources of further information, and the text is well supported by numerous figures and tables.

For the most part chapters are divided into sections on each major disease or group. This layout makes the book, as the title states, a handbook of investigations and not of diagnosis. A typical section opens with some comments on the immunopathogenesis of the condition, lists the investigations of potential relevance, and then enlarges on each of them in turn, discussing the value of the test and the likely significance of possible results. This makes access to information easy for the reader using the book as a quick reference, although a little familiarity with the contents, or use of the index, is necessary to know that, for example, asthma is dealt with under allergic disease rather than respiratory disorders and sudden infant death syndrome under respiratory disorders rather than infections. To a large extent the authors have overcome these inevitable classification problems by the judicious use of repetition and cross referencing.

Reasons a paediatrician may have for performing immunological investigations on a child vary between the extremes of elucidating the underlying defect in a rare and untreatable disorder and detecting a well defined abnormality which indicates an established treatment. In addition, most of us must at some time have experienced the frustration of receiving a result of an immunological test which no-one seems to be able to interpret! This book treads a useful middle path in providing a fairly comprehensive guide to the current repertoire of investigations while emphasising the diagnostic value of some and the uncertain significance of others. It will constitute a considerable improvement on relying on occasional review articles in clinical journals and the ancient edition of Roitt's *Essential Immunology* most of us have lurking on our shelves from medical school days.

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Pediatric Urology. Edited by Keith W Ashcraft. (Pp 540; price not stated, hardback.) W B Saunders Company, 1990. ISBN 0–7216–2746–3.

'These are exciting times' states the opening sentence of Dr Ashcraft's editorial preface to this multiauthor text. Few paediatric urologists or paediatric surgeons would disagree. Paediatric urology, always an interesting and rewarding specialty, has seen a wealth of innovation in recent years: prenatal diagnosis, reconstructive procedures with bowel and artificial sphincters, urinary diversion, laparoscopy, and shock wave lithotripsy all in the space of less than a decade. It is something of a disappointment, therefore, to find that the book itself often fails to convey the excitement of the pace of advance in paediatric urology.

The first few chapters deal with diagnosis, imaging, urodynamics, and the management of urinary infection. I would have liked to have seen an account of the embryological development of the urinary tract. A chapter on renal physiology as it applies to surgical practice would also have been welcome. Chapters 3 to 23 give a thorough account of the various surgical disorders of the genitourinary system in childhood. Some chapters are excellent—notably those on bladder exstrophy, persistent cloaca, urodynamics, and genitourinary tumours. I particularly enjoyed the chapter on paediatric renal transplantation. Dr Hardy Hendren's contribution on urinary undiversion is based on his unrivalled experience and follows his familiar format: surgical principles stated emphatically and the extensive use of illustrations. Here is a surgeon writing for surgeons. In contrast, the chapter on urolithiasis is disappointingly short on surgical detail, although the 'medical' aspects of stone formation are dealt with at length. Hypospadias and the undescended testis form a large part of paediatric urological practice, yet recent advances in these areas are hardly touched upon. Indeed these two chapters could have been written 10 years ago.

Although it has its weaknesses, overall the book emerges as a thorough and competent account of the genitourinary disorders of childhood. At present it has few rivals, with the hugely successful but outdated textbook by Innes Williams and Johnston currently undergoing extensive revision under new editorship.

Dedicated paediatric urologists (a small band in the United Kingdom, but more numerous in the United States and mainland Europe) may be disappointed, but for the paediatric surgeon or paediatrician, *Pediatric Urology* represents a reliable although unexciting source of reference.

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Handbook of Pediatric Oncology. Edited by Roberta A Gottlieb, Donald Pinkel. (Pp 370; £17·95 paperback.) Churchill Livingstone, 1989. ISBN 0–416–32169–9.

This concise yet comprehensive handbook will be a welcome addition to a paediatric oncology ward's bookshelf—if it has not been squeezed into the registrar's pocket. In addition to the wealth of practical information regularly required by junior hospital staff caring for children with cancer, several chapters are also relevant to general paediatricians who share the care of these patients with specialist centres.

The book is divided into sections with further clear subdivisions. The approach to common malignancies is described in the first section with suggested investigations and staging criteria. Treatment protocols are wisely not discussed as they vary with time and among institutions, but the prognosis of tumours is not always easy to find.

Sections on pathological evaluation and therapeutic modalities follow, the latter including up to date chapters on bone marrow transplantation, immunotherapy, and colony stimulating factors. The longest section in the book deals with the complications of cancer and its treatment system by system. This is in some ways too comprehensive for a handbook and the detailed management of cardiac or renal failure could be found in any standard text book. Long term complications are briefly discussed together with psychosocial and family issues. The final section provides an excellent review of the role of genetics in childhood cancer.

The book is well indexed and most chapters are followed by a few key references and suggested further reading. Although published in America, there is little in this book which would not apply equally to patients this side of the Atlantic. Our oncology registrars will simply have to enlarge their pockets.

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The Psychosocial Effects of Bone Marrow Transplantation in Children. By Carien Pot-Mees. (Pp 192; £14:50 paperback.) Eburon Publishers, 1989. ISBN 90-5166-074-X.

Bone marrow transplantation has revolutionised the treatment of a number of haematological, malignant, and genetic disorders. This improvement has not, however, been without cost and this book attempts to analyse the psychological response to the procedure in a group of children treated at Westminster Children's Hospital.

The innovative approach to treatment of many different disorders by bone marrow transplantation by the Westminster team makes them an ideal group to study the nonphysical response to treatment.

The study design is comprehensive and includes a longitudinal assessment of bone marrow transplantation patients as well as a cross sectional comparison between the bone marrow transplantation patients and reference groups (children undergoing open heart surgery and normal, healthy, 'unstressed' children).

For many paediatricians the tests used will be unfamiliar, but the appendices help greatly with interpretation. The results will come as no surprise—an adverse psychosocial effect on children undergoing bone marrow transplantation. What should surprise is the scale of the psychological trauma—for example, 35% of the children exhibiting behavioural disturbance one year after bone marrow transplantation. It is for this reason that this book should be read by all professionals involved in the management of children on bone marrow transplantation units. In addition, as there are implications for other children with chronic illness and those undergoing invasive hospital treatment the book deserves wider reading and I hope it will find its way on to the library shelves of other paediatric units.

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Stable Isotopes in Paediatric Nutritional and Metabolic Research. Edited by T E Chapman, R Berger, D Reijngourd, A Okken. (Pp 317; £40:00 hardback.) Intercept Limited, 1990. ISBN 0-946707-29-4.

Publications of the proceedings of symposia are often unsatisfactory for two reasons. Firstly, the time taken for the book to appear in print often means that the work seems dated and secondly, the patchy quality of the chapters makes the total publication difficult to read and appreciate. This book does not have the first fault, but unfortunately is a good example of the problems associated with multiauthor texts, especially those considering a common topic.

The book follows a symposium of the same title held in Groningen in May 1989. It consists of 32 chapters considering the use of stable isotopes in three broad areas: the nutritional application, the study of intermediary metabolism, and the clinical application in patients with a range of gastrointestinal and metabolic disorders. This is a fair representation of the steady increasing interest in stable labelled tracers as a research tool.

The editors have clearly attempted to introduce a cohesive style, but the text remains repetitive and the subject matter would not be of interest to the majority of general paediatricians. Neonatologists may find interest in the first few chapters, which concern the study of growth and energy expenditure in infants of different age, size, and gestation. Paediatricians and scientists involved in the management of inherited metabolic disease will also find areas of interest, but the book as a whole I suspect will only be of value to the individuals attending the symposium as a reminder of the occasion.

J E WRAITH
Consultant paediatrician

Ultrasound in recurrent abdominal pain

Ultrasound imaging provides a nice, clean, non-invasive, and apparently innocuous test. It is therefore very tempting to use it in children with recurrent abdominal pain 'for reassurance'— of patients, parents, and doctors, but does it tell us anything useful?

Canadian doctors (Shannon *et al*, *Pediatrics* 1990;**86**:35–8) reviewed the studies done on 65 children complaining of recurrent abdominal pain with no clinical indicator of its cause. Although 12 studies showed an abnormality, none was thought to be the cause of the pain and in some cases the discovery was considered to have done more harm than good. Most of the abnormalities were mild and involved either the kidneys or the female genital tract. None was considered to need treatment. In Canada an ultrasound study costs about $C75.

A 'routine' ultrasound study is unlikely to produce an answer. I suspect that most of us will occasionally be pushed into requesting one in the interests of peace.

ARCHIVIST

MEETINGS IN 1991

The 3rd International Conference on Pulmonary Rehabilitation and Home Mechanical Ventilation
10–13 March, Denver
Further details: Adele Gelfand, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206, USA

Clinical Genetics Society
21–22 March, Belfast
11–13 September, Bristol
Further details: Dr Peter Farndon, Clinical Genetics Unit, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG

Paediatric Research Society
5–6 April, Manchester
26–27 September, Newham (London)
Further details: Dr L T Weaver, MRC Dunn Nutrition Unit, Milton Road, Cambridge CB4 1XJ

British Paediatric Association
16–19 April, University of Warwick
Further details: Miss Rosalind Topping/Miss Karen Ingram, British Paediatric Association, 5 St Andrew's Place, Regents Park, London NW1 4LB

British Paediatric Respiratory Group
20–21 September, Manchester
Further details: Dr W Lenney, Royal Alexandra Children's Hospital, Dyke Road, Brighton BN 3JN

Ambulatory Pediatric Association
29 April–3 May, New Orleans
Further details: Marge Degnon, Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101, USA

European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)
27–30 May, Jerusalem
Further details: Dr S Freier, Shaare Zedek Medical Center, Department of Pediatrics, PO Box 293, Jerusalem 91002, Israel

European Paediatric Respiratory Society
June, Rome
Further details: Professor R Ronchetti, IV Pediatric Clinic, University 'La Sapienza', Rome, Italy

European Society for Paediatric Endocrinology
25–29 August, Weimar
Further details: Dr V Hesse, Children's Hospital, Lindenhof, Gotlindenstrasse 2–20, 1130 Berlin, Germany

The 4th Congress of the International Perinatal Doppler Society
29–31 August, Malmö
Further details: Dr K Marsal, Department of Obstetrics and Gynaecology, University Hospital, Lund University, Malmö, Sweden

European Society for Paediatric Research
1–4 September, Zurich
Further details: Professor K Widhalm, Department of Paediatrics, University of Vienna, Wahringer Gurtel 18/20, A-1090 Vienna, Austria

12th European Congress on Perinatal Medicine
12–14 September, Lyon
Further details: CERC, 4 rue Louis-Armand, 92600 Asnieres, France

British Association of Perinatal Medicine
21 September, Edinburgh
Further details: Professor Neil McIntosh, Department of Child Life and Health, 17 Hatton Place, Edinburgh EH9 1UW

4th International Symposium on Pediatric Dermatology
25–28 September, Mazara del Vallo
Further details: Dr Giuseppe Fabrizi, Department of Dermatology, Catholic University of the Sacred Heart, Largo Gemelli, 8–00168 Rome, Italy

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1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1988;**296**:401–50.
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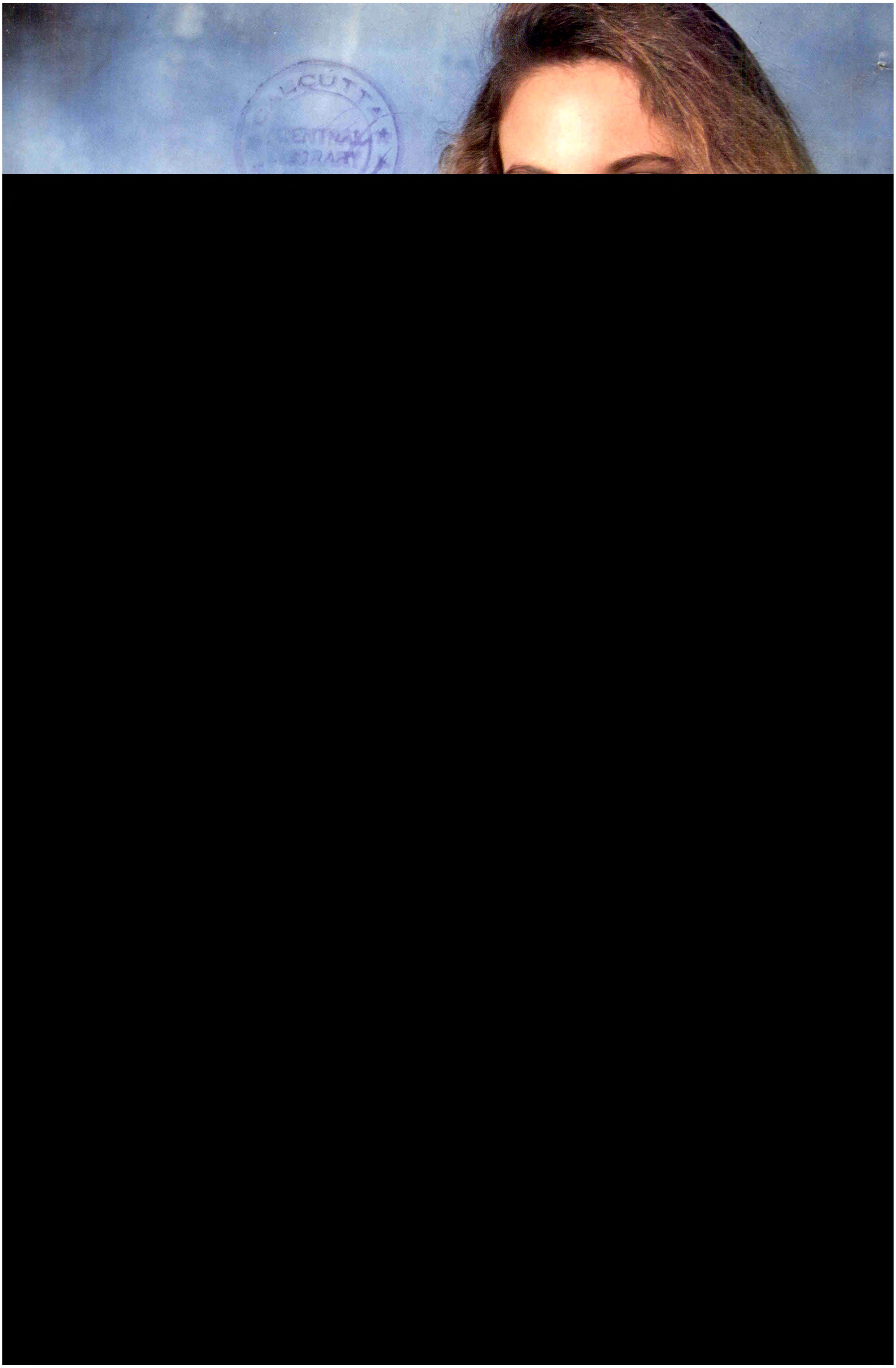

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The Journal of the British Paediatric Association

Annotations

Assisted reproduction and its implications for paediatrics

The relative rarity of multiple birth has made its occurrence in our society a subject of keen interest, sometimes approaching awe. The overwhelming press coverage of the birth and subsequent progress of quintuplets and sextuplets attests to this, but now that these higher multiple births have become, in the eyes of the media, relatively common their newsworthy 'human interest' appeal has proportionately waned. The interest that many feel when hearing of four, five, or six babies born at one time may over-ride other very important considerations related to these births, notably their medical and social implications for the family as well as the hospital and community services. For paediatricians and all those involved with these families it is timely to consider the effects of assisted reproduction in terms of the increasing numbers of higher multiple births and the manner in which they impinge on our services.

From the late 1950s and early 1960s there was a worldwide decline in the number of twins.[1] In the United States this decline was noted somewhat earlier and there was a similar proportionate reduction in the rate of triplet births from the 1930s to the 1940s.[2] These changes appear to be due to reduction in the dizygous twinning rates. In England and Wales (and probably other developed countries) there was an increase in the proportion of triplets and other higher multiple births in the late 1970s.[3] Data from the Office of Population Censuses and Surveys (OPCS) show that in the 15 year period from 1956 to 1970 there were 19 sets of higher multiple births (quadruplets, quintuplets, and sextuplets) and in a similar period from 1971 to 1985 there were 78 sets, a fourfold increase.[3] The increase in the numbers of higher multiple births is certainly due to the introduction of methods for treating the infertile couple and these include ovarian stimulation, gamete intrafallopian transfer (GIFT), and in vitro fertilisation (IVF). Unfortunately, it is neither clear what proportion of triplets and higher multiple births is due to these methods of assisted reproduction, nor the relative importance of each of these techniques to the total number of multiple births.

Assisted reproduction

Infertility may be due to many causes including anovulation, fallopian tube blockage, ovarian underdevelopment, abnormalities of the sperm, and a group where no cause can be found. There is a range of disorders associated with anovulation and drug regimens are available to stimulate the production of ova which are fertilised in the fallopian tube after normal sexual intercourse. Clomiphene citrate is the most widely used drug for ovarian stimulation. Its use alone is often successful in treating the anovulatory woman. Gonadotrophin treatment (either human chorionic gonadotrophin or human menopausal gonadotrophin) may be used in association with clomiphene to trigger ovulation. Hyperstimulation of the ovaries may cause multiple ova to be produced with the risk of multiple birth. Clomiphene alone rarely causes multiple ovulation and the multiple pregnancy rate is in the order of 5%.The risk of multiple pregnancy (twins or more) after gonadotrophin use is considerably higher—in the order of 15–45% and for triplets 5–6%.[4]

GIFT is a new technique, first used successfully in 1984. It appears to be useful in the further management of unexplained infertility. Multiple ova are first harvested laparoscopically after ovarian stimulation. A number of ova are selected for replacement and inserted into the fallopian tube under laparoscopic control together with approximately 10^6 spermatozoa. Success rates for pregnancy are reported to be 25–40% and it is becoming a more widely used technique due to its requirements for relative low technology and low cost. The risk of multiple birth is 19–38%.[5 6]

IVF was initially developed in order to treat the woman with occluded or absent fallopian tubes, but is now more widely used for treating other causes of infertility. The procedure involves harvesting ova after ovarian stimulation as described above. They are then fertilised by spermatozoa outside the body and cultured for a short time. Great care must be taken to maintain the culture environment to ensure normal development during the period of incubation. Fertilised oocytes are carefully inspected and if suitable are replaced in the culture medium until they are inserted into the uterus transcervically at approximately 48 hours from insemination. Unused fertilised ova (now referred to as pre-embryos) may be frozen for insertion at later cycles. The pregnancy success rate for each patient is in the order of 10–15%, and the rate of multiple birth is 22%.[6 7] A recent Medical Research Council report on IVF and GIFT pregnancies indicate that 80% of all such pregnancies occurred after treatment in just three centres; all of which operated outside the National Health Service.[6]

Complications of triplets and higher multiple births

The risk of fetal, neonatal, and infant death is considerably increased in triplets and higher multiple births. In the years 1975–83 the perinatal mortality and infant mortality rates for triplets were 164·5 and 147·7 respectively (England and Wales) compared with mortality rates of 13·8 and 11·7 for singleton births over the same period.[3] For quadruplets the mortality rate was between 40–50% higher than that of triplets. The mortality rates are increased for a number of reasons. These include uteroplacental compromise, premature delivery, and congenital abnormality.

Maternal complications of triplet and higher multiple births include pregnancy induced hypertension, anaemia, and antepartum or postpartum haemorrhage. Routine admission of these women for bed rest is recommended by many obstetricians in the latter part of the second trimester; a practice that is both expensive and disruptive to existing children in the family. In addition, obstetricians may recommend the routine use of tocolytics (usually betamimetics) and regular injections of corticosteroids to the pregnant women in order to avoid excessive uterine activity and enhance fetal lung maturity. Endocervical cerclage has been advocated as a routine procedure in the management of triplets and quadruplets, but the efficacy of this form of management has not been proved. Other fetal risks include placental complications such as abruption, intrauterine growth retardation secondary to placental insufficiency, and malpresentation.

Prematurity is the single most important cause for the increased neonatal mortality in higher multiple births. The incidence of prematurity in triplets is reported to be 88%,[8] and the mean gestational age at which triplets and quadruplets were delivered was 34–35 weeks.[8 9] Despite the surprising degree of maturity in triplets and higher multiples there is a significant number who are born extremely premature and who develop major neonatal complications. It is of some interest that singleton infants born after IVF treatment showed a considerably higher risk of premature delivery than would be expected in a population of naturally occurring pregnancies.[6 7] It is possible that the factors determining infertility are also an additional risk factor for prematurity.

Despite an initial suggestion that infants born as the result of GIFT and IVF were more likely to have congenital abnormality,[10] this has not been confirmed in later studies. Monozygotic twins have a significant risk of cerebral injury, particularly if one twin dies in utero.[11] There is evidence that there is an increased risk of monozygotic twins after the use of ovarian stimulation[12] and IVF.[13] There are very few data on the developmental outcome of the survivors of higher multiple births. A recent study from a tertiary referral centre in Toronto reported follow up data in 84 infants from 29 triplet, quadruplet, and quintuplet pregnancies and found that only one child had a major handicap.[14] Prospectively ascertained cohorts of these infants should be followed up on a geographical basis in order to establish further the quality of life in these high risk children.

Until recently the social aspects of higher multiple births have been largely neglected. The major problems facing these families once the children are home are lack of space and the need for extra help to meet the needs of all the children. The parents of triplets found that their greatest problem was lack of sleep and the unexpected strain on the family finances.[15]

In an effort to understand further the problems associated with grand multiple births, a retrospective study of 'triplet and higher order births' was undertaken which attempted to ascertain all cases over a five year period in the early 1980s. These results have just been published in book form.[16] Both medical and social problems are discussed, but it is the family problems that are most startling. One mother of 6 month old triplets reported that she had calculated that just caring for her babies together with household chores took up 197·5 hours a week, yet there are only 168 hours in each week! Despite this, almost 40% of families with triplets receive no home help from their local authority.

The control of higher multiple births

In view of the apparent considerable increase in the numbers of higher multiple pregnancies, and because these fetuses and babies are at greater risk of death, it is important to consider ways of controlling the number of such deliveries. There are two approaches: applying controls to the assisted reproduction techniques and selective termination of some members of the multiple fetal group. This latter process has been called selective fetocide.

The recent Human Embryology and Assisted Reproduction Act seeks to control centres involved in IVF and carefully limit the numbers of embryos that are replaced to three. This still makes the possibility of triplets likely and some of the embryos may yet divide to monozygotic twins thereby producing quadruplets or possibly more conceptuses. GIFT has been excluded from the legislation and it appears to be an increasingly common form of treatment. Multiple ova (well in excess of three) are inserted in some centres.[5] In my view GIFT should also be more carefully regulated and confined to licensed centres. The major contribution towards the birth of higher multiple births is likely to be ovarian stimulation. This procedure is undertaken in many district general hospitals, possibly without appropriate biochemical or ultrasound control. A strong case can be made for requiring the management of infertility to be confined to subregional centres which are suitably equipped to undertake these procedures in as controlled a manner as possible.

A more controversial approach to the inevitable occurrence of higher multiple pregnancy is termination of selected fetuses, thereby reducing the number from four, five, or six down to one or two. There are now many descriptions in the literature of these techniques. The safest appears to be instillation of potassium chloride directly into the fetal heart through a transabdominal percutaneous needle. This is most successful when performed in the first trimester of pregnancy.[17] Unfortunately this procedure may cause all the fetuses to be lost as the result of premature labour; a particular tragedy for a woman who had been treated initially for infertility. In Britain the legal position of this technique is unclear. It has been suggested that because selective reduction does not cause 'termination of pregnancy', it contravenes the Abortion Act and may subject the operator to prosecution.[18] The American and European experience suggests that selective reduction of multiple pregnancy is a valuable technique in some cases.

The future

There is no reason to believe that there will be a reduction in the steep rise in the numbers of higher multiple births and this continues to cause anxiety to those providing intensive care facilities for premature infants. It is clearly important that the numbers of triplets and higher multiple births continue to be closely monitored. We must also determine the exact contribution that methods of assisted reproduction make to these numbers. In 1989, the British Association of Perinatal Medicine together with the British Paediatric Surveillance Unit surveyed all cases of triplets and higher multiple births delivering after 20 weeks of gestation in Britain in order to determine the proportion due to ovarian stimulation and other techniques. These results will be available soon.

We must establish a dialogue with our gynaecological colleagues who are involved in the treatment of the infertile couple in order to coordinate our efforts. This is particularly

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important in those centres that provide services outside the National Health Service as some of these higher multiple births will require intensive care in inadequately funded health service cots. Perhaps a start could be made if there were agreement that an insurance policy should be taken out by those involved in these forms of treatment to cover the cost of neonatal intensive care should this be required as the result of a higher multiple birth.

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Development of intestinal motility

Normal intestinal motility is essential for the orderly movement of nutrients from one specialised part of the gastrointestinal tract to the next. Disturbances will result in abdominal distension and vomiting when the transit of luminal contents slows down, and in diarrhoea when it speeds up. Under both circumstances the normal digestion and absorption of nutrients and the excretion of waste products will be compromised. In preterm infants, immature intestinal motility is one of the main causes of the 'physiological ileus' that often occurs.[1]

Control of intestinal motility

Patterns of normal intestinal motor activity have been described for most sections of the gastrointestinal tract and it is clear that a hierarchy of controls is responsible for determining the contractile behaviour of the gut.[2] At the lowest level the smooth muscle cells exhibit spontaneous rhythmic electrical activity which determines the timing and frequency of contractile activity. This is further modulated by the action of the enteric nervous system and by the influences of a range of humoral substances that are loosely referred to as 'gut hormones'. The enteric nervous system is essential for the coordination of motor activity, while the gut hormones modulate the tone and excitability of the smooth muscle cells. The sympathetic and parasympathetic limbs of the autonomic nervous system link the enteric nervous system to the nuclei of the brain stem and to higher levels within the central nervous system. The enteric nervous system is complex, containing a similar number of neurones to the spinal cord, and although central connections exist one should think of the enteric nervous system as a autonomous unit that is modulated rather than controlled by the central nervous system.

The cells that ultimately form the enteric nerves migrate from the neural crest during the first trimester, and after colonisation of the gut they undergo a prolonged period of maturation that is in part determined by the microenvironment in which they find themselves.[3] Evidence from animal studies suggests that these enteric neurones remain 'plastic' and open to environmental influences until a relatively late stage in their development.[4] Histological and ultrastructural studies show the presence of enteric nerves and smooth muscle cells within the wall of the human intestine during the second trimester, and by 22 weeks' gestation the small intestine is 'histologically mature'.[5] From clinical experience, however, we know that the intestines of preterm infants are often intolerant of enteral feeds, indicating that immaturity in the development of motor control is often a limiting factor in our ability to feed by the enteral route.[1] Our present understanding of the development of these controls is outlined below.

Sucking and swallowing

The actions of sucking and swallowing a feed rely on the integration of control between a larger number of cranial nerve nuclei and are clearly dependent on the maturation of brain stem function. Swallowing has been observed in utero as early as 16 weeks' gestation and from studies using red blood cells tagged with ^{51}Cr injected into the amniotic fluid we know that the volume of fluid swallowed increases from 13 ml/day at 20 weeks to 450 ml/day at full term.[6] It must be remembered, however, that the fetus is immersed in a bath of amniotic fluid and does not have to coordinate swallowing with either sucking or the protection of the airway. In preterm infants sucking movements are generally feeble but by 34–35 weeks' gestation a mature nutritive sucking pattern has developed.[7 8]

Gryboski was the first to outline the normal patterns of oesophageal motility in both term and preterm infants.[9] In adults a swallow initiates relaxation of the upper oesophageal spincter so that food can be carried along the length of the oesophagus by a primary peristaltic wave to the lower sphincter, which then relaxes to allow its passage into the stomach.[10] While this pattern is present in full term infants who suck effectively, the motility of the oesophageal body in preterm infants is characterised by poorly propagated, low pressure biphasic contractions.[9] These will be inefficient at clearing refluxing fluids from the oesophagus and are in many ways similar to the disordered activity that is commonly seen in children with cerebral palsy.[11]

The lower oesophageal sphincter has an important role in preventing the regurgitation of fluid from the stomach and in preterm infants the pressure gradient between the fundus of the stomach and the lower oesophagus is reduced. With increasing maturity this pressure gradually rises as a result of the increased contractile activity of the intrinsic smooth muscle of the sphincter and the extrinsic diaphragmatic muscle, and of the increasing length of the intra-abdominal oesophagus.[12] In small preterm infants chronic respiratory disease that leads to increases in intra-abdominal pressure, and drugs such as theophylline that lower sphincter pressure,[13] will conspire to increase greatly the risks of reflux and aspiration. The apparent late development of nutritive sucking acts to protect the oropharynx and oesophagus at a time when controls may not have adequately developed to cope with the passage of fluids.

The stomach

In clinical practice it is easy to bypass the mouth and oesophagus and to deliver milk directly into the stomach through a nasogastric tube. It is, however, clear that the emptying of liquids from the stomach is not normal in preterm infants and feeds often have to be delivered directly into the jejunum before they will be tolerated. No systematic study of the ontogeny of gastric emptying has been carried out but in preterm infants (as in adults) the gastric emptying of liquids decreases as the energy density of the feed increases.[14] This explains why infants may tolerate a half strength feed while a full formula feed results in gastric stasis, abdominal distention, and vomiting. It seems likely that in the immature gut this inhibitory feedback, which is mediated by both neural and humoral mechanisms, is set at a level of increased sensitivity. Manometeric studies have shown that the pressures generated by spontaneous contractile activity in the gastric antrum increase with increasing gestational age,[15] and results of interventional studies have suggested that non-nutritive sucking may increase enteral food tolerance, presumably through a vagally mediated reflex.[16]

The small intestine

The small intestine has clearly defined cyclical patterns of contractile activity when fasting,[17] which in older children or adults are completely disrupted after a meal when they are replaced by more random mixing activity. Studies using implanted electromyographic electrodes to record small intestinal contractile activity in utero in fetal lambs have shown that, at a time equivalent to 28 weeks' gestation in humans, activity is random and of low amplitude with the progressive development of more organised propagative activity during subsequent weeks, until at full term a mature cyclical pattern has developed.[18] In human preterm infants an identical developmental progression of fasting activity has been shown to occur with manometric recording.[15] This preprogrammed pattern of development, which is almost certainly dependent on the maturation of neural connections within the enteric and central nervous system, has also been seen in cows and dogs. In dogs, which are neurologically immature at birth, fasting small intestinal motility is less well developed than in the more mature sheep, cows, or humans.[19] These links between small intestinal motility and the integrity of the central nervous system are further supported by the observations that birth asphyxia and hydrocephalus reduce the rate of duodenal contractile activity in human preterm infants and by the similar cycle times during fasting motor activity and rapid eye movement sleep.[20]

The motor response of the small intestine to food is not only a function of the volume and nutritional density of the food, but is also determined by the sensitivity of the gut to these stimuli. In preterm infants the length of time that the gut is exposed to food is an important determinant factor, implying that the humorally mediated postprandial motor response is upregulated by previous luminal nutrition.[21] The idea that early feeding is beneficial to intestinal function is not new and gut hormone concentrations[22] and brush border digestive function[23] are potentiated by luminal nutrients.

The colon

Little is known about the development of the motility of the colon in humans. The colon probably plays little part in the circulation of swallowed amniotic fluid. In utero, and for most newborns their first bowel motion occurs either during or within 48 hours of birth. In preterm infants slowing of colonic motility may result in constipation and this may lead by enteroenteral reflexes to delays in gastric emptying. Anecdotal observations have suggested that glycerine suppositories may indirectly increase enteral food tolerance by promoting rectal evacuation.

Conclusions

The development of motor activity at all levels within the gastrointestinal tract is broadly similar. After migrating from the neural crest to their final destination in the wall of the intestine, the cells that form the enteric nervous system undergo many months of maturation. Disruption of this migration or alterations to the environment of these cells may lead to loss of function with the development of motility disorders such as intestinal pseudo-obstruction or Hirschsprung's disease. In preterm infants this maturation is incomplete, and noxious stimuli such as sepsis or acidosis may disrupt the immature motor controls and lead to reduced contractile activity and intolerance of feeds. In addition to the development of intrinsic controls, the central nervous system and the circulating gut hormones have important roles in modulating intestinal motor activity. It is the integrity and normal development of these controls that is required before young infants are able to tolerate a full oral nutrient intake safely.

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ORIGINAL ARTICLES

Doppler assessment of pulmonary artery pressure and extrapulmonary shunting in the acute phase of hyaline membrane disease

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Abstract

The natural history of pulmonary artery pressure and extrapulmonary shunting in acute hyaline membrane disease was studied by serial Doppler echocardiography in 57 preterm infants, 38 with, and 19 without, hyaline membrane disease. Pulmonary artery pressure was assessed non-invasively by its inverse relationship with the ratio of pulmonary artery Doppler time to peak velocity: right ventricular ejection time. The mean ratio was significantly lower in the infants with hyaline membrane disease. The mean ratio for each infant with hyaline membrane disease varied widely and did not correlate with criteria of maturity or severity of disease. Individual ratios correlated with arterial pH. Between 60–80 hours after birth, 14 of 18 infants with hyaline membrane disease (78%) and one of 19 without (5%) had patent ductus arteriosus. Left to right and bidirectional shunting at ductal and atrial level were common; pure right to left shunting was uncommon. The mean ratio seen with bidirectional shunting was significantly lower than that seen with left to right shunting. Ratios and patterns of extra pulmonary shunting were similar when the fractional inspired oxygen (F_IO_2) was >0·9 compared with when it was <0·9.

Pulmonary artery pressure is high during the acute phase of hyaline membrane disease but varies widely among infants. A few infants have extrapulmonary right to left shunting, and these infants are difficult to detect clinically.

Early studies implicated persistent pulmonary hypertension that leads to right to left shunting of blood through extrapulmonary channels in both the pathogenesis of hyaline membrane disease and as a factor contributing to the subsequent hypoxaemia.[1] Subsequent studies using direct[2] and indirect[3] methods of assessment showed that raised pulmonary artery pressure was a consistent feature of severe hyaline membrane disease. Catheter studies, however, have shown that in most infants less than 10% of total right to left shunt occurs through extrapulmonary channels.[4 5] Tolazoline used as a pulmonary vasodilator leads to improvement in oxygenation in some infants with severe hyaline membrane disease,[6] but has a high incidence of serious complications.[7] There is a need therefore to be able to diagnose those with appreciable right to left shunting through the ductus arteriosus and foramen ovale so that we can identify those who are most likely to respond to pulmonary vasodilators.[8]

Doppler echocardiography provides a non-invasive means by which to assess pulmonary artery pressure and extrapulmonary shunting. The ratio of pulmonary artery time to peak velocity: right ventricular ejection time (TPV:RVET) as measured from the Doppler waveform, has a close inverse correlation to pulmonary artery pressure.[9] This method has two main advantages over the right ventricular systolic time intervals derived from M mode echocardiography that were used in other indirect studies of pulmonary artery pressure in hyaline membrane disease.[3] Firstly, in validation studies it has shown much closer correlation to pulmonary artery pressure.[9 10] Secondly, Doppler echocardiography permits us to study blood flow patterns through the ductus arteriosus and foramen ovale at the same time as making an indirect assessment of pulmonary artery pressure. To our knowledge such Doppler studies have not previously been undertaken in hyaline membrane disease. The aim of this study therefore was to use these methods to compare the natural history of pulmonary artery pressure and extrapulmonary shunting in preterm infants with and without hyaline membrane disease. In this paper we looked specifically at the results during the acute phase of hyaline membrane disease; subsequent measurements taken during the recovery phase will be reported separately.

Subjects and methods

All infants were studied with an ATL Ultramark 4 scanner with range gated pulsed wave Doppler. Two dimensional imaging was done with a 7·5 MHz transducer incorporating a 5 MHz pulsed Doppler crystal.

The procedure for each study was as follows: the pulmonary artery was visualised from the parasternal long axis view. The Doppler sample volume was placed just distal to the pulmonary valve and the pulmonary artery velocity pattern was recorded. The pattern was frozen on screen and the time intervals measured using the incorporated Doppler measurement calipers; a print was then taken. TPV was measured as the time interval between the systolic Doppler waveform leaving the baseline and reaching its peak velocity. RVET was the time interval between the systolic waveform leaving its peak velocity and returning to the baseline. A mean of three systolic waveforms was taken. A second 'blind' observer repeated the measurements on 50 of the Doppler prints using a computer digitiser system. The correlation coefficient between 'on line' and 'blind' measurements was 0·92.

The ductus arteriosus was then visualised

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from the high left parasternal ductal view. The Doppler sample volume was placed in the pulmonary end of the duct and the flow pattern recorded. The duct was classified: as 'closed' when it could not be visualised and no Doppler flow could be recorded; as 'restrictive' when it could not be visualised or there was a localised area of constriction but Doppler flow could be recorded; and as 'wide open' when it could be seen to be clearly patent throughout its course and Doppler flow was recorded.

Finally, the atrial septum was visualised from the subcostal four chamber view; the Doppler sample was placed in the foramen ovale and the flow pattern was recorded.

Fifty seven preterm infants were studied, 19 healthy infants without hyaline membrane disease and 38 infants with hyaline membrane disease. The healthy infants had a mean gestation of 31·8 weeks (range 28–34) and a mean birth weight of 1610 g (range 950–2050). The healthy infants had minimal or no extra oxygen requirements; two infants were initially placed in low concentrations of oxygen, but both were breathing air by 24 hours. The healthy group of infants were studied initially during the first 12 hours after birth and then at 24 hour intervals until a steady state TPV:RVET ratio was achieved.

The infants with hyaline membrane disease had a mean gestation of 30·5 weeks (range 26–37) and a mean birth weight of 1570 g (range 580–2960). The differences in birth weight and gestation between the two groups were not significant. The criteria for the severity of respiratory disease are shown in table 1. The infants with hyaline membrane disease were studied as soon as possible after birth and then at least at 24 hour intervals. At the time of each study, records were kept of oxygen treatment, ventilator settings, most recent pH and blood gas measurements, and directly measured blood pressure. The results comprise those measurements made during the acute phase of hyaline membrane disease, which was defined as the time until the fractional inspired oxygen (F_IO_2) had peaked and returned to below 0·5.

Statistical analysis was by Student's unpaired *t* test, χ^2 test, and linear regression analysis. A p value of <0·05 was accepted as significant. The study was approved by the Central Oxford Research ethics committee.

Table 1 Criteria of severity of hyaline membrane disease in 38 affected infants, 36 of whom were treated with artificial ventilation

No with maximum F_IO_2:	
<0·6	5
0·6–0·9	16
>0·9	17
Mean (range) maximum F_IO_2	0·8 (0·35–1·0)
Mean (range) maximum mean airway pressure (cm H_2O)	12·8 (5·5–25·5)
Mean (range) length of acute phase (hours)	82 (12–241)
Median (range) length of time on ventilator (hours)	184 (58–5880)

Table 2 Number of studies carried out in each age group. Some infants had more than one study in a particular group

Age group (hours)	*Infants with hyaline membrane disease (n=38)*	*Infants without hyaline membrane disease (n=19)*
0–6	12	10
7–14	11	8
15–24	19	6
25–36	18	13
37–48	21	6
49–72	20	18
73–96	6	13
>96	13	19

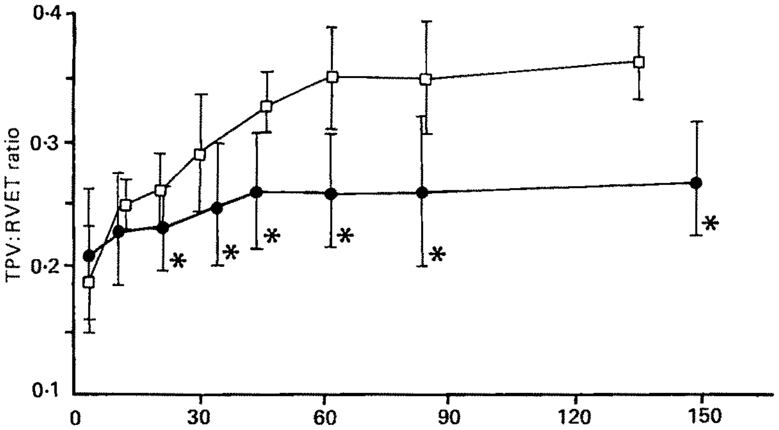


*Figure 1 Comparison of the change in mean (SD) time to peak velocity: right ventricular ejection time (TPV:RVET) ratio in preterm infants with (solid circles) and without (open squares) hyaline membrane disease. *=p<0·05.*

Results

TPV:RVET RATIO

To compare changes in TPV:RVET ratio in infants with and without hyaline membrane disease, the studies were grouped by postnatal age. The number of studies in each age group is shown in table 2. In fig 1 the mean (1 SD) ratio has been plotted at the mean measurement time. In the infants without hyaline membrane disease, the mean ratio rose over the first 72 hours of life, and then remained constant. In contrast, the mean ratio in the acute phase of hyaline membrane disease rose slightly during the first 24 hours, with only a small increase after that time. Within the first six hours, the mean (SD) TPV:RVET ratio was 0·21 (0·05) in the infants with hyaline membrane disease and 0·195 (0·04) in those without; this difference was not significant. After 15 hours in all groups the mean ratio was significantly less in the infants with hyaline membrane disease. By 73 to 96 hours, the mean ratio was 0·26 (0·06) in those with hyaline membrane disease compared with 0·35 (0·045) in those without (p<0·01). There was a wide variation in ratios among individual infants in the group with hyaline membrane disease. Examples taken from the lower, middle, and upper part of the range are shown in fig 2. To measure this variation, the mean TPV:RVET ratio was calculated for the acute phase in each infant: this ranged from 0·175 to 0·34 with an overall mean of 0·25. The mean ratio during the acute phase of hyaline membrane disease in each infant showed no significant correlation with gestation, birth weight, maximum F_IO_2, or the length of the acute phase. Individual ratio measurements also showed no significant correlation with F_IO_2, peak inspiratory pressure, or mean airway pressure at the time of the study, but did show a

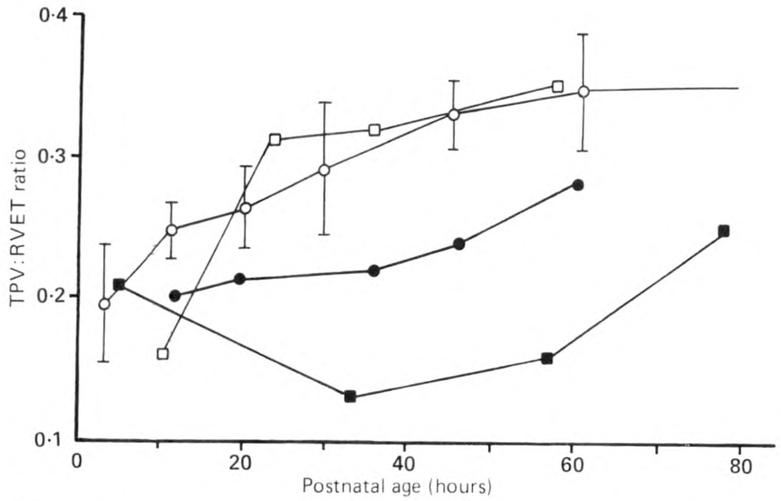


Figure 2 Examples of longitudinal change in time to peak velocity: right ventricular ejection time (TPV:RVET) ratios in three infants with hyaline membrane disease. Gestational ages and maximum inspired oxygen concentrations were: 34 weeks, 80% (open squares); 29 weeks, 100% (solid circles); and 36 weeks, 100% (solid squares). For comparison, changes in mean (SD) TPV:RVET ratio for healthy preterm infants are shown (open circles).

weak but significant correlation with the most recent arterial pH (r=0·24, p<0·01).

DUCTUS ARTERIOSUS

The incidence of ductal closure with age is shown in the two groups of infants in table 3. Within the first 20 hours only one duct, in an infant with hyaline membrane disease, was found to be closed. In the infants without hyaline membrane disease, ductal closure was complete in 18 of 19 studies (95%) by 60–79 hours. In contrast, in the infants with hyaline membrane disease, only four of 18 studies (22%) showed a closed duct within this time period (p<0·01). In the infants with hyaline membrane disease the patent ducts tended to get smaller with age; 15 of 26 studies in the first 19 hours showed a wide open duct (58%) compared with three of 18 studies between 60–79 hours (17%).

Table 3 Number (%) of studies in each age group that showed a closed ductus arteriosus. No infant had more than one study in each group

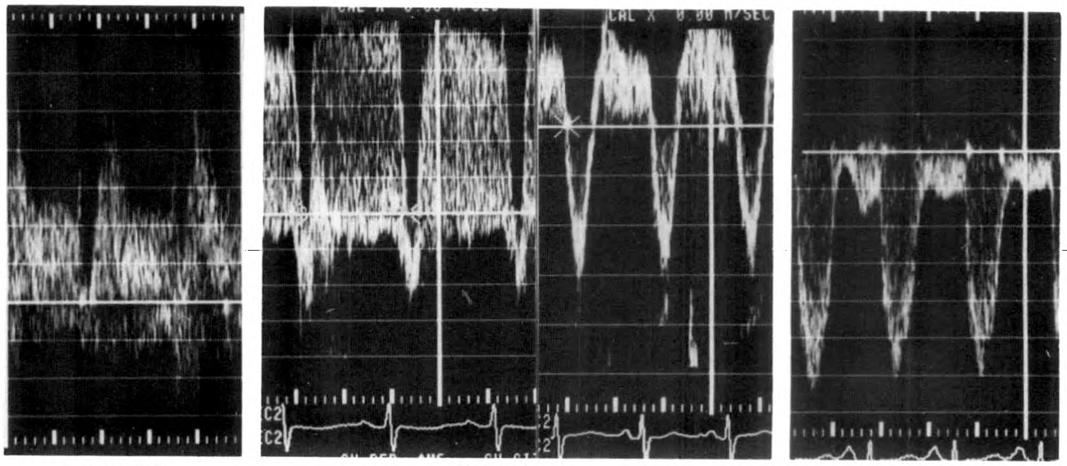
Age group (hours)	Infants with hyaline membrane disease	Infants without hyaline membrane disease	p Value
0–19	1/26 (4)	0/17	Not applicable
20–39	6/27 (22)	10/19 (53)	0·03
40–59	5/27 (19)	15/17 (88)	<0·001
60–79	4/18 (22)	18/19 (95)	<0·001

Table 4 Number (%) of studies showing each pattern of Doppler flow through the ductus arteriosus in each age group

Age group (hours)	Left to right	Bidirectional	Right to left
0–19 (n=25)	14 (56)	10 (40)	1 (4)
20–39 (n=21)	12 (57)	8 (38)	1 (5)
40–59 (n=22)	15 (68)	7 (32)	0
60–79 (n=14)	12 (85)	2 (14)	0

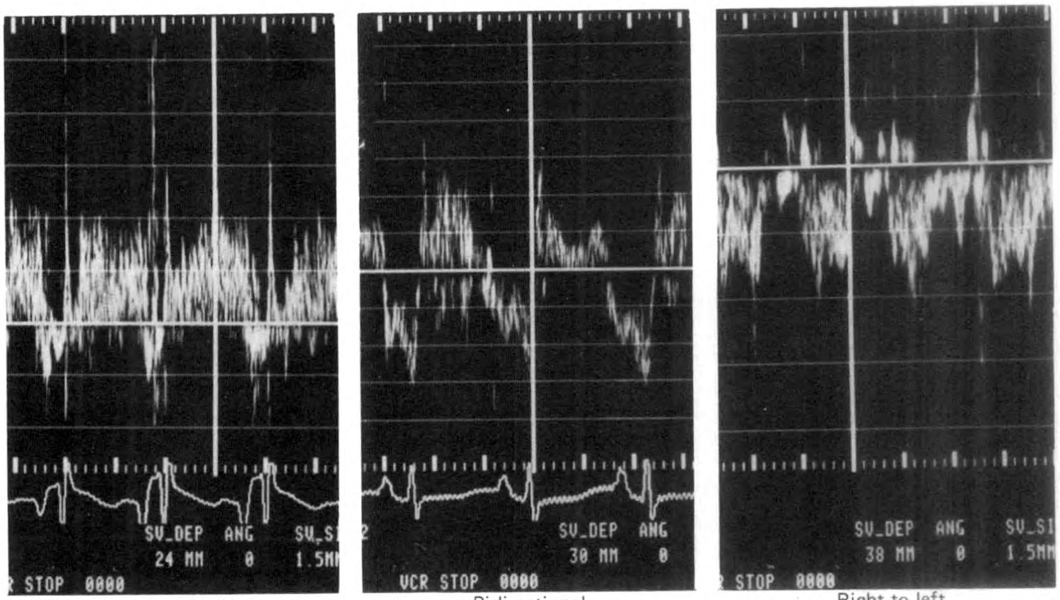
Three Doppler velocity time patterns of flow through the ductus arteriosus were seen (fig 3): left to right, in which flow was left to right through the cardiac cycle; an early systolic cessation of flow as seen in fig 3 was often a feature of this pattern; bidirectional, in which early systolic flow was right to left with a variable degree of late systolic and pandiastolic flow was from left to right; and right to left, in which flow was in this direction through the cardiac cycle. In the infants without hyaline membrane disease, the flow was left to right in all but five of the nine studies done in the first eight hours, when it was bidirectional. Within the first 19 hours in the infants with hyaline membrane disease flow was left to right in 56% of studies, with just one study (4%) showing right to left flow; in the remainder (40%) the flow was bidirectional (table 4). By 60 to 79 hours, 85% showed left to right flow with just two studies showing bidirectional flow. Only two of the 120 studies in the infants with hyaline membrane disease showed right to left flow.

In studies in which the duct was closed the TPV:RVET varied between 0·16 and 0·40 (mean 0·28). Mean (SD) TPV:RVET ratio in studies with left to right ductal shunt was 0·25 (0·045), which is significantly higher than those with bidirectional shunts (0·225 (0·045), p<0·001), and those with right to left shunts (0·215 (0·021), p<0·005). In the studies with



Left to right Bidirectional Right to left

Figure 3 Doppler flow patterns through the ductus arteriorsus. Positive deflection represents left to right flow and negative deflection right to left flow. In the bidirectional group there are two examples illustrating an increasing proportion of the cardiac cycle occupied by right to left shunting.



Left to right Bidirectional Right to left

Figure 4 Interatrial Doppler flow patterns. Positive deflection represents left to right flow and negative deflections right to left flow.

bidirectional shunting there were considerable variations in the length of right to left shunting within the cardiac cycle. This was measured with the incorporated Doppler measurement calipers as the time between which the right to left Doppler flow left and returned to the baseline. This time was then expressed as a ratio to the RVET (right–left:RVET ratio), to standardise for different heart rates. In the studies with bidirectional ductal shunting, the right–left:RVET ratio ranged from 0·125 to 1·0 (mean 0·52). The right–left:RVET ratio correlated significantly with the TPV:RVET ratio ($r=-0{\cdot}55$, $p<0{\cdot}0001$) and F_IO_2 at the time of study ($r=-0{\cdot}53$, $p<0{\cdot}0001$) but no correlation was found with mean systemic blood pressure. Of ducts with bidirectional right to left flow, 97% were classified as 'wide open' compared with only 17% of these with left to right flow.

ATRIAL SHUNTING

For practical reasons it was not possible to get good quality Doppler studies of interatrial flow in all cases; the number of studies of interatrial flow are therefore less than for ductal flow. Some degree of incompetence of the foramen ovale was detected in all infants whose studies were satisfactory. Some bidirectional flow was seen in all studies. For analysis the studies were divided into three patterns (fig 4). (1) Left to right: maximum left to right flow was seen in ventricular systole and early diastole with cessation of flow or small right to left flow in mid to late diastole. (2) Bidirectional: right to left flow extended from late diastole into early systole with left to right flow in late systole and early diastole. (3) Right to left: the right to left flow dominated throughout most of the cardiac cycle.

Data on atrial shunting was obtained in only seven of the healthy infants because of incompleteness of the early studies. In all studies in these infants the flow was predominantly left to right. Within the first 20 hours in the infants with hyaline membrane disease four studies (31%) showed bidirectional flow, one study showed right to left flow (8%), and the remaining eight (62%) showed left to right flow (table 5). The percentage showing bidirectional flow rose to 61% (n=11) between 20 to 39 hours and fell to 25% (n=2) between 60 and 79 hours. Just two studies showed predominantly right to left flow.

Mean (SD) TPV:RVET ratio in the studies with left to right flow was 0·27 (0·05); this was significantly higher than those with bidirectional flow 0·23 (0·04), $p<0{\cdot}001$, and those with right to left flow, 0·19 (0·035), $p<0{\cdot}05$.

The matching of atrial and ductal patterns of shunting in studies where both were satisfactorily recorded is shown in table 6. In studies where ductal shunting was left to right or bidirectional, 21 of 34 studies (62%) showed identical patterns of atrial shunting. In the one ductal study with right to left shunting where the atrial shunt was also recorded the atrial flow was also right to left.

Table 5 Number (%) of studies showing each pattern of Doppler flow through the foramen ovale in each age group

Age group (hours)	*Left to right*	*Bidirectional*	*Right to left*
0–19 (n=13)	8 (62)	4 (31)	1 (8)
20–39 (n=18)	7 (39)	11 (61)	0
40–59 (n=17)	8 (47)	8 (47)	1 (6)
60–79 (n=8)	6 (75)	2 (25)	0

Table 6 Matching of patterns of ductal and interatrial Doppler flow. Data are expressed as number (%) of studies

	Direction of interatrial flow		
	Left to right	*Bidirectional*	*Right to left*
Direction of ductal flow:			
Left to right (n=34)	21 (62)	13 (38)	0
Bidirectional (n=21)	7 (33)	13 (62)	1 (5)
Right to left (n=1)	0	0	1 (100)

SEVERE HYALINE MEMBRANE DISEASE (F_IO_2 >0·9)

The data were analysed separately in the 28 studies in which the F_IO_2 was >0·9. The mean (SD) TPV:RVET ratio in this group was 0·25 (0·04), which was identical to the mean in the studies in which the F_IO_2 was <0·9—that is, 0·25 (0·05). Ductal patency and flow were recorded in all 28 studies: five (18%) were closed, 12 (43%) showed left to right flow, 10 (36%) showed bidirectional flow, and one (4%) showed right to left flow. Interatrial Doppler flow was satisfactorily recorded in 15 of these studies: six (40%) showed left to right flow, eight (53%) showed bidirectional flow, and one (7%) showed right to left flow.

Two infants in this group received intravenous tolazoline; both had been studied in the 12 hours before receiving the drug. One responded with a fall in F_IO_2 from 1·0 to 0·8. The most recent TPV:RVET was 0·13 with obvious right to left components to bidirectional shunting at ductal and atrial level. The other did not respond. The most recent TPV:RVET was 0·27 with left to right shunting at ductal and atrial level. Neither infant was studied at the time that the drug was given.

Discussion

Our results show that indirectly measured pulmonary artery pressure remains significantly higher in preterm infants during the acute phase of hyaline membrane disease than in those with no respiratory problems. This is consistent with the findings of previous authors who used both direct and indirect methods to assess pulmonary artery pressure in infants with severe hyaline membrane disease.[2 3] Moss *et al* using direct measurements within 48 hours of birth, found a mean pulmonary artery pressure of 45 mm Hg in infants with hyaline membrane disease compared with 32 mm Hg in those without[2]; in those with hyaline membrane disease pressures varied between 28 and 58 mm Hg. In our study the suggested pulmonary artery pressure also showed a wide degree of variation among infants, with the lowest pressures well within the normal range. Unlike Halliday *et al*,[3] however, we found no correlations between indirectly assessed pulmonary artery pressure and indices of infant maturity or disease severity. It would therefore be difficult to predict those with the highest pulmonary vascular resistance solely from clinical variables.

Many factors influence pulmonary vascular resistance.[11] For example, hypoxaemia and acidosis are both potent vasoconstrictors.[12] The pH and blood gases were not measured at the time of the study, but were the most recent measurements. This, combined with the frequent rapid fluctuation in oxygen tension, means that we are not able to comment on the influence of hypoxia. There was however, no correlation with F_IO_2 at the time of study. pH changes less rapidly, and there was a weak but significant correlation with TPV:RVET ratio. Mechanical factors have also been suggested as a cause of increased pulmonary vascular resistance. High positive end expiratory pressures increase both extra pulmonary shunting in immature animals[13] and hypoxia in human newborns.[14] End expiratory pressures of more than 5 cm H_2O were not used in this study, but there was no association between TPV:RVET and mean airway or peak airway pressure.

Prostaglandins seem to play an important part in the changes in pulmonary vascular resistance that occur after birth. As gestation advances and immediately after birth the balance of vasoconstrictor and vasodilator prostaglandins shifts towards the vasodilators.[11] Studies of circulating prostaglandins and their metabolites in hyaline membrane disease have been contradictory. One study showed an increase in the constrictor prostaglandin $F_{2\alpha}$,[15] another correlated higher metabolic concentrations of the dilator prostacyclin with increasing severity of respiratory disease.[16] It may be that the balance between dilator and constrictor prostaglandins determines the variable pulmonary artery pressure observed in the infants in this study.

In healthy preterm infants the ductus arteriosus usually closes within the first three days of life.[17] This study shows that 80% of infants with hyaline membrane disease have patent ducts throughout the acute phase of the illness. Thus it seems that respiratory disease is an important factor in the development of prolonged ductal patency. Hypoxia, and possibly increased levels of ductal dilatory prostaglandins,[18] may combine with reduced ductal muscle mass and reduced oxygen induced vasoconstriction,[19] to maintain patency in these preterm infants. This study did not attempt to correlate ductal patency with physical signs. Anecdotally, however, we have observed that murmurs were present in only a few cases and were usually associated with high velocity turbulent left to right shunts, often through a quite constricted duct.

Bidirectional flow through the ductus is seen when pulmonary artery pressure is slightly less than aortic.[20] The early systolic right to left flow is probably a reflection of two factors. Firstly, that proximity to the heart means that pressure rises earlier in systole at the pulmonary than at the aortic end of the duct. Secondly, the fact that in pulmonary hypertension systolic pressure may rise relatively more than diastolic, producing a peak pressure briefly in excess of aortic peak pressure.[20] This study has shown that as pulmonary artery pressure rises so the duration of right to left flow increases. When pulmonary artery pressure is less than aortic throughout the cardiac cycle, so the flow will be left to right. This pattern was seen in most of the studies throughout the acute phase of hyaline membrane disease; mean TPV:RVET was significantly higher than in those with bidirectional flow. There was a considerable degree of overlap suggesting that pulmonary artery pressure may not be the sole determinant of flow pattern. Relative aortic pressure is important as well as the size of the duct and resistance to flow; almost all the ducts with bidirectional flow were widely patent. High pulmonary pressure is not always associated with a patent duct, however.

Low TPV:RVETs were seen when the ducts were closed.

Pressure differences between the atria through the cardiac cycle are complex and have been well documented in children with atrial septal defects.[21] In these children maximum left to right shunting occurs in late ventricular systole and early diastole, and in almost all cases there are two periods of minimal or right to left flow: firstly, after the atrioventricular valve has opened in mid to late diastole and, secondly, at the onset of ventricular contraction in early systole. The Doppler patterns correlate closely with this, though the right to left flow in early systole was less commonly seen. With higher right sided pressures, the right to left flow in late diastole and early systole merged to produce a more bidirectional pattern. We confirmed that a small amount of right to left flow occurs across atrial communications even when the right sided pressures are normal.

In this study, we have looked at patterns of flow and did not attempt to calculate extra pulmonary right to left shunt size or its contribution to systemic hypoxia. This study has shown, however, that even when the F_IO_2 was more than 0·9, 60% of examinations showed either no flow or left to right flow through the duct, and 40% showed left to right flow at atrial level. In the remainder the right to left flow occupied only a small part of the cardiac cycle. We therefore confirm previous studies that showed that the main site of right to left shunting in most infants with hyaline membrane disease is probably intrapulmonary.[4,5] A small proportion of infants show appreciable extra pulmonary right to left shunting, particularly during the first 48 hours, and it is likely that these are the infants who will produce the best response to pulmonary vasodilators.[8] Identifying these infants using clinical variables is not possible.

We hope that the methods described in this study will identify those that are most likely to respond to pulmonary vasodilators and might also make further investigations of the haemodynamic effects of these drugs in hyaline membrane disease easier.

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Cyclical variations in cerebral blood flow velocity

M Y Anthony, D H Evans, M I Levene

Abstract

Because little is known about spontaneous changes in cerebral blood flow in neonates, a newly developed online Doppler technique was used to insonate continuously the middle cerebral arteries of a group of sick (n=20) and full term healthy (n=16) newborn infants for a period of one minute. A total of 290 recordings of epochs each lasting one minute were analysed, and pronounced regular, cyclical variations were seen in the velocity traces of these infants. The cycles occurred 1·5–5 times/minute and were present for at least one epoch in all 20 of the sick infants and in 15 of the 16 healthy mature neonates. Simultaneous recordings of the systemic blood pressure in the sick infants rarely showed the same cyclical variations. The cyclical variation is different from the beat to beat variability seen in the waveforms previously described, and is an additional factor to account for the wide variation in 'normal' velocity recordings obtained when Doppler ultrasound is measured over a short period of time.

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Measurements of cerebral blood flow velocities by Doppler ultrasound are being increasingly used to study the neonatal cerebral circulation. The information obtained may help us to understand the pathophysiological processes that predispose to neonatal cerebral injury. We have previously reported the development of an online Doppler technique in which the transducer can be applied directly to the skin overlying the middle cerebral artery. The cerebral blood flow velocity is then measured continuously for a period of one minute.[1] [2] Many previously reported studies have used intermittent, short duration Doppler monitoring; this can analyse only 30 cardiac cycles of data at most. In some of these methods errors have been caused by movement of the Doppler transducer during the studies, and inconsistency in the angle of insonation between the observations. The use of continuous monitoring of velocity for a long period of time seems to provide new information on the variability of the cerebral blood flow velocity signal that has not been previously reported to our knowledge.

Patients and methods

DOPPLER ULTRASOUND

The Doppler ultrasound system used in this study is a modification of the method we have previously described.[2] A 4 or 6 MHz Doptek pulsed wave button transducer (11 mm×7 mm×5 mm) was fixed to the skin over the baby's temporal bone at the point where the Doppler signal from the ipsilateral middle cerebral artery (MCA) was maximal. A soft Stomahesive wafer (ConvaTec Ltd) was applied to the skin of the temples as this clings without the need for additional adhesive. The transducer was then secured to the wafer with collodion, the Stomahesive protecting the infant's delicate skin from the collodion. The Doppler sample volume, depth, and length was then adjusted electronically to optimise the signal. Once in place the transducer can remain fixed for up to four hours before being removed.

The probe was connected by a fine coaxial cable to a Doptek pulsed wave Doppler unit, which in turn was connected to a digital signal processing unit and a Nimbus microcomputer. The computer automatically switched the system on at predetermined intervals (in this case every 20 minutes) and gathered 60 seconds of both Doppler signals and (in babies with indwelling arterial lines) blood pressure signals. It was possible to override the automatic timing sequence and capture 60 seconds of data at will. The digital signal processing unit carries spectral analysis on the Doppler signal in real time and stores a new range together with the corresponding blood pressure reading every 12·5 ms. The data are then analysed beat by beat to produce a list of values including the systolic, mean, and diastolic values of the maximum frequency envelope and the systolic, mean, and diastolic values of blood pressure for each cardiac cycle. These values were then written to floppy disk and graphed on the Nimbus screen.

The whole unit is transportable and can be wheeled to the cot side. The study was approved by the hospital ethics committee, and informed consent was obtained from at least one parent before each study.

PATIENTS

Two groups of infants were studied: those who required neonatal intensive care (group 1) and a cohort of normal healthy newborn babies who were nursed on the postnatal ward with their mothers (group 2).

The infants in group 1 all had indwelling arterial catheters or cannulas for clinical monitoring before entry into the study so that continuous blood pressure readings could be obtained. All babies in this group required mechanical ventilation at the time of the first study. A morphine infusion or pancuronium, or both, were used when clinically indicated. All the infants were continuously monitored with either an indwell-

Table 1 Details of sick infants

Gestational age (weeks)	*No of infants*	*Weight range (g)*
≤30	12	780–1220
31–34	7	1040–2170
>34	1	2820

Table 2 Details of studies of cerebral blood flow velocity

	Group 1	*Group 2*
No of babies studied	20	16
No of studies carried out	32	16
No of 1 minute epochs	241	49
No of babies with cyclical variations	20	15
No (%) of epochs containing cyclical variations	149 (62)	30 (61)
Maximum percentage variability	64	52
Range of percentage systolic change	10–64	11–52
Median percentage systolic change	23	24

ing arterial oxygen electrode or an oxyhaemoglobin saturation monitor that was applied across the infant's hand. Arterial blood gas tensions were measured before and after each study.

Results

A total of 36 infants were studied, 20 in group 1 and 16 in group 2. The median gestational age of the sick infants in group 1 was 29 weeks (range 24–37), and their median birth weight was 1150 g (range 780–2820). Twelve of the infants in group 1 were 30 weeks' gestational age or less (see table 1). Eleven babies were studied on one day only, six on two separate days, and three on three separate days, making a total of 32 studies. The postnatal ages at the start of each study ranged from 2 hours to 8 days. The length of any one study on a baby ranged from one and a half hours to four hours depending on the quality of the Doppler signal and the baby's clinical condition.

All the infants in group 2 were healthy. Their gestational ages ranged from 37–42 weeks (median 39) and they were all studied at postnatal ages ranging from 1–7 days. All the infants in group 2 were appropriate weights for their gestational ages. No healthy infant was studied on more than one occasion and no study lasted more than two hours. The median number of epochs recorded on each infant in group 2 was three (range 1–6). The infants had been fed 1–2 hours before the study, and most were either asleep or in a quiet awake state.

A total of 290 epochs each lasting 60 seconds were analysed. Visual examination of the one minute tracing showed pronounced variability over the course of the recording. There were two types of variability: the first was the beat to beat variability that was described by Perlman *et al* and is illustrated in fig 1,[3] and the second was a pattern of regular cyclical variation in the signal with a frequency of between 1·5 and 5/minute (fig 2). We referred to this pattern as 'cycling'. Most babies had both patterns within the same recording.

The frequency of the cycling was counted as the number of phases present within each epoch of one minute. The degree of variability was calculated by taking the maximum systolic velocity of a cycle (a) and subtracting the minimum systolic velocity of the same phase (b) and dividing by the maximum systolic velocity ((a–b)/a). This was expressed as a percentage. Where the beat to beat variation made the value of (a) or (b) obscure, the cycling variability was not measured although the underlying frequency was obvious on inspection (see table 2).

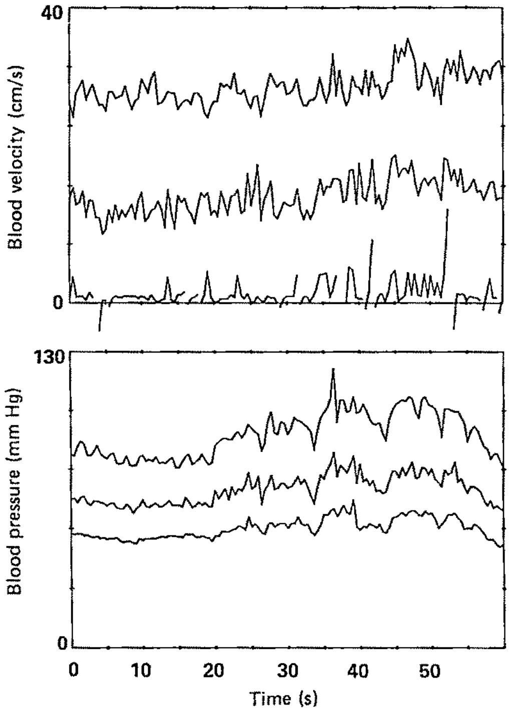

Figure 1 Marked beat to beat variability in blood pressure and cerebral blood flow velocity traces.

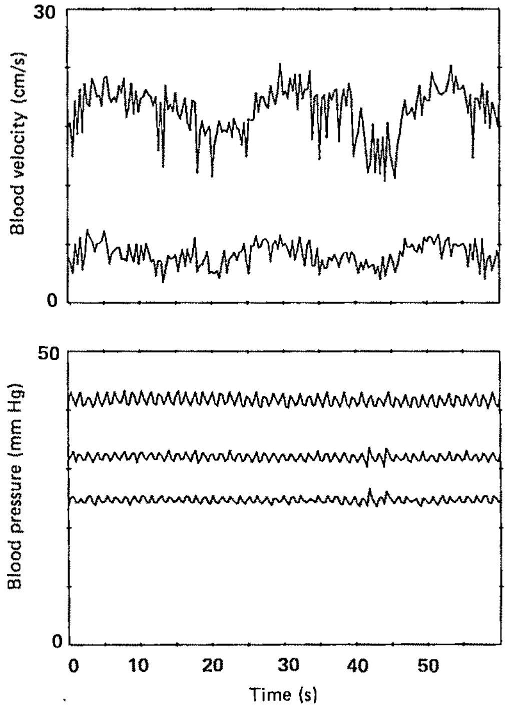

Figure 2 Cyclical variability in cerebral blood flow velocity at 3 cycles/minute with superimposed beat to beat variability. The blood pressure trace shows spikes coinciding with the ventilator inflations at 50 breaths/minute. Diastolic cerebral blood flow is zero.

GROUP 1

All 20 babies in group 1 showed cyclical variation at some time, although the variability and frequency of the cycling varied among babies and even within the same baby during different epochs. Only one baby did not show any cyclical variation during one complete study of one and a half hours (six epochs), but did show cycling changes during a study the following day. Only two of the 20 babies had cyclical variation during every 60 second epoch, although these were in the shorter studies.

Of the 241 epochs analysed, cycling episodes occurred in 149 (62%). The frequency varied from 1·5 to 5 cycles a minute; this refers both to individual babies at different epochs and among the different babies. In some babies cyclical variation was not present during one epoch but was seen during the next epoch 20 minutes later.

The cycling variability of the systolic velocity could be calculated in 103 epochs and ranged between 10% and 64% (median 23%). The cycling variability altered from baby to baby and from epoch to epoch within the same baby. Among the infants in group 1 there seemed to be no correlation between the presence or frequency of cycling or the gestational age or the severity of the infant's illness. Out of the total of 32 studies, infants received pancuronium alone (n=8), morphine alone (n=11), both (n=2), or neither (n=11). There were no differences in the number or variability of cycles when the use of these two drugs was compared.

In many cases the blood pressure recordings made at the same time as the cerebral blood flow velocity recordings did not show any variability (fig 2). In eight studies there was pronounced beat to beat variability (fig 1) and all the ventilated babies showed increases in blood pressure that coincided with the ventilator inflations (fig 2). Cycling was seen on the blood pressure traces of seven babies (fig 3). This usually occurred during more than one epoch in each of the babies who showed this cyclical blood pressure change, but none showed it continuously. Of the seven babies, two were well breathing air on low rate ventilation without sedation, and five were sedated with morphine or pancuronium and had high ventilation requirements; one of the five was also receiving a dopamine infusion. When cycling was seen in both blood pressure and cerebral blood flow velocity recordings the cycles were never in exact phase nor of the same frequency (fig 3).

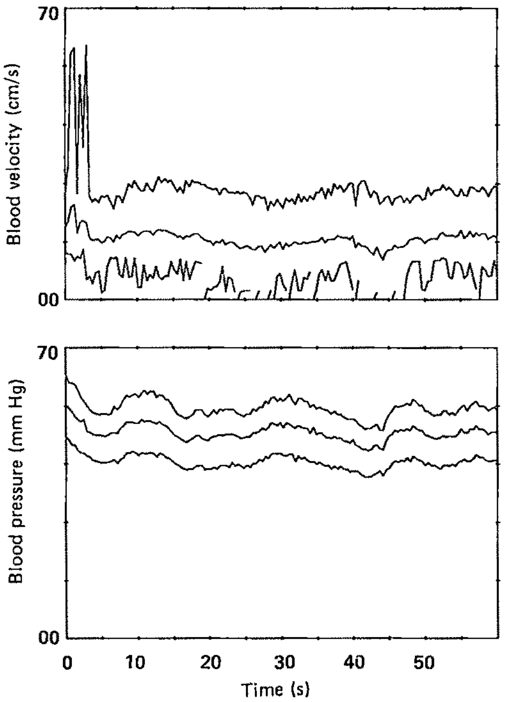

Figure 3 Cyclical variability of both cerebral blood flow velocity and blood pressure at different frequencies.

We could find no relationship between the cycling seen in the Doppler traces and any of the other variables measured. In particular, there were no significant differences in the infant's heart rate measured at the highest and lowest systolic phases of the cycle. There were no consistent changes in arterial oxygen concentration or haemoglobin saturation recordings during the course of the cycles, which might have accounted for the variations seen. The cycling was not abolished by the infusion of plasma.

GROUP 2

Of the 16 babies in this group, 15 showed cycling at some time, and the frequency varied from 1·5 to 5/minute. A total of 49 epochs were studied of which 30 showed cycling (61%). These healthy term infants showed the same degree of beat to beat variability in their velocity traces as the sick and preterm infants.

The cycling variability could be calculated in 20 cycles. The median percentage systolic change during cycling was 24·2% (range 10·7–51·6%). The heart rate did not alter during the phase of the cycles. Cycling occurred in infants who were either awake or asleep. It was not possible to measure blood pressure directly in this group and indirect oscillometric methods for recording blood pressure were not possible because they are intermittent, and when the cuff was inflated the infant was disturbed.

There was no difference in the variability between the sick and the full term healthy infants (p=0·11).

Discussion

This study shows that there is a common pattern of regular cyclical variation most clearly seen in systolic cerebral blood flow velocity and occurring at a frequency of 1·5 to 5 cycles/minute. The cycles are present in both sick extremely preterm and healthy full term neonates during the first eight days of life. The babies that we studied cover a wide range of gestational ages and were studied up to eight days of postnatal life. We do not have data beyond eight days, and are unaware of any studies containing such data.

Cowan has described this cyclical variability in 18 healthy, 5 day old, full term neonates undergoing sleep studies,[4] but she could not relate her findings to rapid eye movement sleep nor to abnormality on the electroencephalogram. Not all the babies in our study were sleeping, and cycling was also present in those who were awake. Two studies of the adult cerebral circulation using periods of continuous Doppler recording lasting up to 10 minutes did not report similar cycling variability.[5 6]

Two infants in group 1 had haemodynamically important patent ductus arteriosus and required treatment with indomethacin. In neither case was a diastolic component of the sonogram recorded. Five other infants in group 1 also had heart murmurs consistent with patent ductus arteriosus but were not thought to have a haemodynamically important lesions; no infant in group 2 had a cardiac murmur. The cycling pattern was seen at some time in all but one of the 36 infants studied and there were no differences in either the frequency or the amplitude of the cycles between babies with and without murmurs or the two with symptomatic patent ductus arteriosus. It is most unlikely that a patent ductus has any influence on the cycling phenomenon.

There are two possible causes of these cycles: local factors associated with vessels and cerebral events. The diameter of the vessels, and therefore blood velocity, is influenced by various local factors including the arteriolar concentration of carbon dioxide, catecholamine concentrations, neural factors, and myogenic reflexes within the vessel wall.[7] Among the sick infants studied here, many had been given a non-depolarising muscle blocker (pancuronium) to inhibit spontaneous respiration. There were no changes in ventilator rate during epochs, and it is therefore unlikely that there was a cyclical change in the carbon dioxide tension that caused the regular changes in cerebral blood flow velocity that we observed.

Little is known about the fine control mechanisms of the cerebral vasculature. For autoregulation to occur there must be a feedback mechanism that causes a change in arteriolar size in response to changes in the cerebral blood flow. In most of the infants studied there was no change in blood pressure at the time of the regular cycling cerebral blood flow velocity pattern. It seems unlikely that the effect we saw was the result of a passive myogenic response secondary to systemic changes in either cardiac output or peripheral resistance.

It is possible that this is a fairly primitive phenomenon and we suggest that the cycling in velocity may be an immature response that represents an underdamped autoregulatory mechanism. The cycles may represent rhythmical changes in cerebral vascular tone with a 'hunting' effect on the underlying cerebral blood flow velocity and presumably on cerebral blood flow. This may disappear with cerebral maturation, but it will be of interest to study older infants with this technique to discover at what age the cycling disappears. Although it is most likely that the small cerebral arterioles are responsible for the cycling, it is also conceivable that there may be rhythmic changes in tone of the major cerebral arteries. There is some evidence that in adults the major cerebral arteries play a part in cerebral autoregulation.[8] The Doppler technique will not be able to distinguish changes in velocity arising as a result of either large or small arteriolar changes.

One must also consider that the cyclic activity may also be the result of more widespread cerebral events such as seizures or cerebral oedema. Seizures are associated with pronounced changes in cerebral blood flow and intracranial pressure. It is possible that cyclical changes in cerebral blood flow velocity may be the result of seizure activity, but were not found by Cowan who made continuous electroencephalographic recordings during her Doppler studies.[4] As these changes were also seen in 15 out of 16 healthy full term infants, seizures are most unlikely to have been the cause. Lundberg described cyclical changes in intracranial pressure at 0·5–2 cycles/minute in adults and referred to them as 'B' waves.[9] These changes were of irregular amplitude and interval and were associated with stupor or coma. If the patients were aroused the B waves became less regular or disappeared. They were also associated with Cheyne-Stokes breathing and would disappear once the patient was ventilated. We have also seen regular fluctuations in intracranial pressure in critically ill full term asphyxiated infants.[10] The frequency of these fluctuations was about 0·5 cycles/minute, but all the infants were extremely ill and all died. Cerebral oedema is also most unlikely to have caused the cyclical variation in our babies, none of whom had severe birth asphyxia.

The beat to beat variability described by Perlman *et al* was measured in the anterior cerebral arteries of premature infants being ventilated for respiratory distress.[3] This variability was reflected in the simultaneously recorded blood pressure and was associated with an increased risk of intraventricular haemorrhage. The same workers later showed that this variability was abolished by muscle relaxing drugs.[11] They concluded that lack of synchrony between the infants' respiratory efforts and the ventilator was responsible for the beat to beat fluctuations in both blood pressure and cerebral blood flow velocity. Rennie *et al* have shown that there is a reduction in the beat to beat variability in cerebral blood flow velocity in ventilated preterm infants once synchronous breathing is established,[12] and Rennie has shown that the variability can be reduced by cardiovascular support with either dopamine or plasma infusions.[13] The variability was greatest within the first 12 hours of life and then gradually reduced over the next 36 hours.

The cycling variability that we have described in this report is quite different from the beat to beat variability described by Perlman *et al* and Rennie *et al*, but the illustrations of the velocity and blood pressure recordings clearly show that this form of beat to beat variability is superimposed on the rhythmical cycling variability at 1·5 to 5 cycles/minute.

The most immediate clinical relevance of this observation with respect to further Doppler studies is in the error that may occur if velocity data are recorded over short periods of time. Almost all published studies that have used Doppler techniques during the neonatal period have collected data for 30 consecutive cardiac impulses at most (about 15 seconds). This is one factor in the high intraobserver variability. As both systolic and diastolic frequencies seem to vary to the same degree, cycling variability will be reflected to a much lesser extent by measurements of the resistance or pulsatility indices. These indices correlate less well with changes in cerebral blood flow than measurements of the peak systolic velocity, end diastolic velocity, or area under the velocity curve.[14 15]

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Gastrointestinal blood flow velocity after the first feed

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Abstract

Twenty preterm infants (gestational age range 27–36 weeks) who had never been fed enterally were studied. Doppler indices of flow velocity from the superior mesenteric and coeliac arteries were measured immediately before, and at postprandial time intervals up to 60 minutes after, a first feed of 1 ml of milk given through a nasogastric tube. There were no significant differences between the preprandial and postprandial values of blood pressure, heart rate, oxygen and carbon dioxide tensions, and pH.

The median peak systolic velocity (PSV) (55·9 cm/sec) and time average mean velocity (TAV) (10·6 cm/sec) before the feed at the superior mesenteric artery rose progressively and significantly to postprandial peaks of 88·5 cm/sec and 20·5 cm/sec at 45 minutes, respectively. Significant postprandial rises in the median PSV and TAV values at the coeliac artery were also observed, with a peak at 45 minutes. There were no significant correlations between blood flow velocity indices (preprandial or postprandial) and gestational age, postnatal age, conceptional age, or birth weight.

We conclude that the first exposure of preterm babies to a small volume of milk feed is associated with postprandial changes in blood flow velocity consistent with an increase in blood flow in the superior mesenteric and coeliac arteries, although the mechanism of this response is uncertain.

It is the practice in many neonatal units to delay the introduction of enteral feeding in preterm infants if they are unwell. Basal plasma concentrations of certain gut hormones,[1 2] postprandial surges in their plasma concentrations,[3 4] and the postprandial motor response of the small intestine[5] in preterm infants are to some extent dependent on the magnitude of previous exposure of the gut to milk feeds.

Doppler ultrasound measurements of flow velocity in the superior mesenteric artery have been reported in adults[6 7] and more recently in preterm infants.[8] To our knowledge there have been no reports of postprandial flow velocity in abdominal vessels in response to the introduction of a uniform, small bolus of milk in preterm infants who have not previously received enteral feeds. Recently Leidig reported postprandial changes in flow velocity from the superior mesenteric arteries of preterm infants, but most of these infants had already been established on enteral feeds and their postprandial flow velocity was measured after varying volumes of bolus feed.[8]

In our neonatal unit it is usual to start milk feeding in very preterm babies with bolus volumes as small as 1 ml at hourly intervals. It is not uncommon for the nurses to observe self correcting hypoxaemic episodes (on transcutaneous monitoring), with or without bradycardias and apnoeas, within a few hours of the start of feeding that resolve when feeding is temporarily discontinued. It was not the purpose of this study to explore the relationship of these episodes to postprandial changes in flow velocity in gastrointestinal arteries. Instead, we wished to determine whether in very preterm babies of different postnatal ages, the first enteral feed of a very small bolus of milk was associated with postprandial changes in Doppler flow velocity measured at the superior mesenteric and coeliac arteries.

Patients and methods

We studied 20 preterm infants (seven girls and 13 boys) whose weight and age characteristics are shown in table 1. Although some had previously been treated for respiratory distress none had ever shown signs or symptoms of intestinal disease and all were apparently healthy at the time of the study with no clinical signs of patent ductus arteriosus. Umbilical catheters had been removed at least 24 hours before the start of the study. None of the infants had previously received any food enterally.

A nasogastric feeding tube (deadspace 0·25 ml) was passed and after a 30 minute period of stabilisation, baseline Doppler blood flow velocities in the superior mesenteric and coeliac arteries were measured. Each baby was then 'fed' with 1·25 ml of milk introduced through the nasogastric tube. Sixteen babies received a modified cows' milk formula, and the remainder expressed breast milk, according to the mother's preference.

Blood flow velocity measurements from both arteries were repeated at 5, 15, 30, 45, and 60 minutes after this first feed. At the time of each Doppler measurement the heart rate and blood pressure (Dinamap) were recorded for each baby. In five of the 20 infants peripheral arterial

Table 1 Median (range) ages and birth weights of the 20 babies

Gestational age (weeks)	29 (27–36)
Birth weight (g)	1248 (910–2480)
Postnatal age (days)	7 (1–33)
Conceptional age (weeks)	31 (28–37)

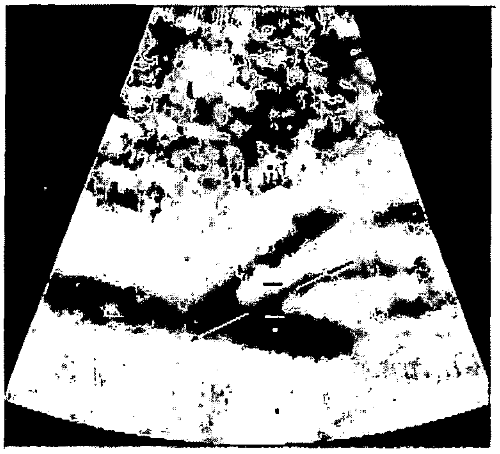

Figure 1 Longitudinal abdominal ultrasound scan showing the coeliac and superior mesenteric arteries as they arise from the aorta. Doppler sample gate is positioned at the origin of the superior mesenteric artery.

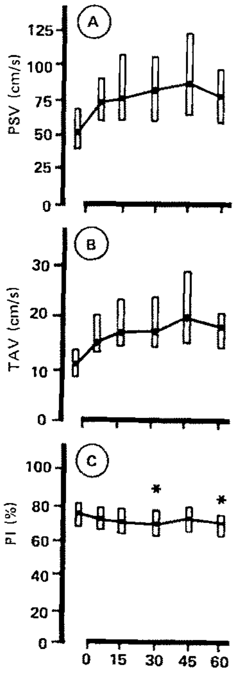

Figure 2 Median and interquartile ranges of: (A) peak systolic velocity (PSV); (B) time average mean velocity (TAV); and (C) Pourcelot resistance index (PI) measured from the superior mesenteric artery, before the feed (0 minutes) and at different postprandial times. At each postprandial time, the median PSV and TAV were significantly higher than before the feed ($p<0{\cdot}01$); $^*p<0{\cdot}05$ compared with before the feed.

catheters had been left in position and in these babies we measured oxygen and carbon dioxide tensions and pH before, and 60 minutes after, the feed.

MEASUREMENTS OF BLOOD FLOW VELOCITY

Recordings were made with a duplex ultrasound scanner (Acuson 128) equipped with a S519 probe, which has a pulse echo frequency of 5·0 MHz and a Doppler frequency of 5·0 MHz. The high pass wall filter was set at 125 Hz and the ultrasound intensity was kept to a minimum compatible with the collection of an adequate signal (always less than 150 mW/cm^2 spatial peak, temporal average).

The superior mesenteric and coeliac arteries were visualised through longitudinal abdominal scans using real time imaging, which allowed placement of the Doppler sample (gate size 3 mm) roughly 5 mm distal to the origin of each artery from the aorta (fig 1). The system allowed for an automatic 'angle correction' to 0° in the velocity calculations.

The maximal Doppler signal was obtained both visibly and audibly. The system permitted up to 20 consecutive cardiac cycles to be captured and analysed by fast fourier transformation. In practice, the quality of the Doppler signal could rarely be maintained to capture this number of consecutive cycles. On average we were able to analyse 10 consecutive cycles, and in no baby did we analyse less than five cycles.

The built in microcomputer permitted immediate analysis of the frozen velocity waveform, and the indices chosen for the study were the peak systolic velocity (PSV), the time average mean velocity (TAV) and the Pourcelot resistance index (PI), which was defined as (S–D) divided by S, where (S) is the maximum systolic frequency shift, and (D) the minimum diastolic frequency shift. This is believed to be an index of vascular resistance downstream from the point of Doppler insonation.

REPEATABILITY OF METHOD AND STATISTICAL METHODS

We assessed the repeatability of the method by making 50 paired blood flow velocity recordings, five minutes apart, from both the superior mesenteric and coeliac arteries in healthy, sleeping, preterm babies who had never been fed orally. The ultrasound probe was removed between examinations. From each artery, we calculated the mean value of paired measurements of PSV, TAV, and PI (n=100) and the SD of the difference between pairs (n=50). We also calculated the corresponding coefficient of variation of these measurements with 0·95 probability. In the study analyses, the significance of differences between preprandial and postprandial measurements was tested by the Wilcoxon signed rank test (two tailed level of significance is quoted). The significance of the correlation between the various ultrasound measurements and gestational age, postnatal age, conceptional age, and birth weight was tested by Kendall's rank correlation.

Results

In our assessment of repeatability the mean values of measurements of PSV, TAV, and PI from the superior mesenteric artery (in each case n=100), and the SD of the difference between pairs, were 62·5 (4·6 cm/sec); 18·0 (1·3 cm/sec), and 69·0 (3·1%). The corresponding results expressed as coefficients of variation with 0·95 probability were 15%, 14%, and 9%, respectively. Similar results were obtained from the coeliac artery: mean values (SD of difference between pairs) for PSV, TAV, and PI were 67·3 (4·3 cm/sec); 19·0 (1·2 cm/sec), and 66 (3·4%), with corresponding coefficients of variation with 0·95 probability of 13%, 13%, and 10%.

The median PSV and TAV from the superior mesenteric artery before the feed were 55·9 cm/sec and 10·6 cm/sec, respectively, and rose to a postprandial peak of 88·5 cm/sec and 20·5 cm/sec at 45 minutes (fig 2). Similarly in the coeliac artery PSV and TAV rose from median values before the feed of 61·5 cm/sec and 18·3 cm/sec, respectively, to postprandial peaks of 108·0 cm/sec and 31·5 cm/sec at 45 minutes (fig 3). At each postprandial interval the median PSV and TAV from each artery were significantly higher than before the feed ($p<0{\cdot}01$). In individual infants the blood flow velocity peaked at different times. Table 2 shows the time interval after the feed when babies had their maximal increases in PSV and TAV measured in the superior mesenteric artery. In most infants the peak velocity occurred at 45 minutes after the feed. Similar changes were observed from the coeliac artery.

The median PI before the feed in the superior mesenteric artery was 76%, and this fell postprandially to a significantly lower value at 30 minutes (69·5%) and 60 minutes (71%) ($p<0{\cdot}05$) (fig 2). We did not observe any significant change in PI measured from the coeliac artery (fig 3).

There was no correlation between blood flow velocity indices (preprandial or postprandial) on the one hand, and gestational age, postnatal age, conceptional age, or birth weight on the other. There were no significant differences between preprandial and postprandial values of blood

Table 2 Postprandial timing of maximum peak systolic velocity and average mean velocity measured in superior mesenteric artery in 20 babies

Postprandial time (mins)	*Maximum peak systolic velocity*	*Time average mean velocity*
5	2	0
15	2	1
30	4	7
45	11	9
60	1	3

pressure, heart rate, or oxygen and carbon dioxide tensions and pH.

In only four of the 20 infants was feeding subsequently stopped, and in all but one of these the decision was made because of episodic bradycardia. We did not observe any difference in the blood flow velocity patterns between infants in whom we subsequently withdrew feeds and those who continued to feed. It was not the purpose of this study to compare the influence of different milks on blood flow velocity, but the four infants who received expressed breast milk had similar trends in their flow velocities as the infants who received formula milk.

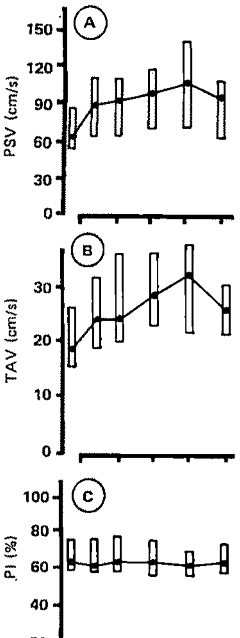

Figure 3 Median and interquartile ranges of: (A) peak systolic velocity (PSV); (B) time average mean velocity (TAV); (C) Pourcelot resistance index (PI) measured from the coeliac artery, before the feed (0 minutes) and at different postprandial times. At each postprandial time, the median PSV and TAV were significantly higher than before the feed (p<0·01).

Discussion

It is common clinical practice to start oral milk feeds in preterm babies with boluses as small as 1 ml. Changes in blood flow velocity in the superior mesenteric artery and coeliac axis after the first exposure of the gut to an extremely small volume of milk have not previously been measured. We observed a rise in flow velocity from both Doppler sampling sites in all infants following the 1 ml feed, and the maximum PSV and TAV was observed at 45 minutes in most infants.

We accept that in this study, the Doppler measurements were not made 'blind' (the observer being aware of the timing and nature of the feed), and to try and remove any 'operator bias' we aim to undertake further studies in which the observer is unaware of whether 1 ml of milk, air, sterile water, or no feed at all has been introduced down the nasogastric tube.

We think that our observations represent genuine changes in flow velocity for the following reasons. Firstly, at each time interval measurements were made in a uniform way. There is no reason to suppose that measurements made at 45 minutes 'disturbed' infants any more than the previous measurements. Nor is there any reason to suppose that measurements made at 60 minutes (when flow velocities fell) caused less 'disturbance' than the measurements at 45 minutes. Secondly, there were no significant changes in heart rate of blood pressure throughout the study. Thirdly, the changes in flow velocities that we recorded were similar to those reported in adults after a meal, and consistent with the findings of Norryd *et al* who used a dye dilution method with catheterisation of the superior mesenteric artery and showed that in adults, flow increased within 15 minutes of the start of a meal.[9]

Leidig measured changes in PSV, TAV, and PI from the superior mesenteric artery in preterm babies, but most of these infants had already been exposed to milk feeds and measurements were made after varying volumes of bolus feeds.[8] He also observed that PSV and TAV rose by 15 minutes after the feed and peaked at 45 minutes. These changes were associated with a fall in PI. It was further observed that 'basal' flow velocities were higher in infants who had received larger volumes of milk. All infants had started feeding within 24 hours of birth with volumes according to postnatal age. It was, therefore, not possible to know whether postnatal age (or conceptional age) or previous 'milk loading' influenced basal flow velocities. As none of the infants in our study had previously received milk, basal flow velocity measurements were independent of exposure to feeds. None the less, we observed no correlation between any of the Doppler indices of flow from either artery with postnatal or conceptional age.

The control of intestinal blood flow in adults is complex and is determined by local regulatory mechanisms that are independent of neural control (metabolic and myogenic); extrinsic regulation (autonomic nervous system); and by circulating vasoactive substances.[10] Virtually nothing is known about the development of these regulatory mechanisms in fetal life and early infancy. We consider it unlikely that the increase in flow velocities observed after the small volume feed was related to an increase in small intestine motor activity, because Bisset *et al* observed disruption of fasting motor activity only after large bolus feeds in infants who had already been well established on oral feeds.[5]

It is important to note that similar changes were observed when measurements were made from both the coeliac axis and the superior mesenteric artery, consistent with there being an increase in blood flow to the stomach as well as the small intestine. Qamar *et al*, using a duplex scanning system, showed that there was an immediate increase in coeliac axis flow velocity that persisted for 10 minutes and returned to resting levels by 30 minutes in adults after the ingestion of a liquid meal.[11] In dogs a small increase in coeliac axis blood flow was observed after intragastric placement of food.[12]

In our study the relationship between coeliac axis flow and superior mesenteric flow is unclear, although the time course of the rise after the 1 ml feed was similar, peaking at 45 minutes. We did not observe a significant effect on PI measured from the coeliac axis after the feed, although PI fell when measured from the superior mesenteric artery. If it is true that PI is an index of 'downstream' resistance, then a Doppler sample from the coeliac axis will reflect splenic and hepatic vascular resistance as well as the resistance of the gastric arterial bed. In this respect it is of interest that radioisotope imaging after a bolus injection of technetium in adults showed that there was a reduction in splenic and hepatic arterial flow during digestion.[13]

The fact that a rise in flow velocity was observed as rapidly as five minutes after the introduction of the feed suggests that there is a flow regulatory mechanism operating—at least initially—in the stomach. It is possible that mechanical stimulation of the gastric mucosa by the milk bolus triggered the changes in blood flow velocity through a local reflex. Certainly mechanical stimulation of a denervated jejunal segment causes an increase in blood flow, a response which is probably not limited to the mucosa and which is blocked by 5-hydroxytryptamine.[14] If mechanical stimulation of the gastric mucosa was in part responsible for triggering the changes in flow velocity then there is no reason to suppose that the feeding tube itself was responsible as this was left in position undisturbed throughout the study.

A number of gastrointestinal and pancreatic polypeptide hormones such as secretin, cholecystokinin, and glucagon have been shown to increase intestinal blood flow in adults,[10] but the diversity of the experimental conditions is such that it is difficult to draw conclusions about a physiological role for any of these hormones in the regulation of intestinal or gastric blood flow. Certainly in preterm infants, following the first feed of human milk, plasma glucagon concentration did not rise.[3]

The synthetic analogue of gastrin, pentagastrin, is a potent intestinal vasodilator,[10] but little is known about the vasomotor effects of gastrin in a physiological setting. Although term babies have a postprandial rise in plasma gastrin concentration during the hour after the first milk feed,[15] a postprandial response is not observed in preterm babies until 13 days postnatal age, even though they are already receiving regular milk feeds.[4] Preterm babies, 6 days old, who had never received milk, had lower basal plasma concentrations of gastrin compared with those of an equivalent age who had been fed.[1] Fourteen of the 20 infants in our study had their first bolus feed and flow velocity measurements at a postnatal age of 8 days or less. Based on the observations cited above, even if gastrin was a gastrointestinal vasodilator it is unlikely that a postprandial surge in plasma gastrin was implicated in the observed rise in flow velocities.

Whether the changes in flow velocity we have observed in this study are initiated by a stimulus arising in the stomach or beyond the stomach (or both) is unclear. This could probably be clarified by repeating these studies with a small bolus of feed introduced through a transpyloric tube.

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Evaluation of a taurine containing amino acid solution in parenteral nutrition

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Abstract

Vaminolact, an amino acid solution containing taurine, was given to 15 sick newborn babies. They were compared with a group of 10 babies who received a solution that did not contain taurine (Vamin glucose). Efficacy and safety were evaluated by monitoring plasma amino acid patterns, growth patterns, nitrogen balance, and biochemical and haematological profiles. No serious abnormalities in amino acid concentrations were found. After an initial fall the taurine concentration recovered more rapidly in those receiving the taurine supplement, though this difference was not significant. Phenylalanine concentrations were within the reference range in the group receiving Vaminolact, and were significantly lower than in the group receiving Vamin glucose. Metabolic acidosis, which occurred in several subjects in each group, was not a serious problem. Liver function tests remained satisfactory. Nitrogen retention was greater among those receiving Vaminolact than in the control group.

Vaminolact is a safe and effective amino acid solution for use in critically ill babies.

Total parenteral nutrition is now an integral part of the care of sick newborn infants, particularly those for whom enteral feeding is unsuitable becuase they have respiratory distress, gastrointestinal anomalies, or necrotising enterocolitis.

Recently, amino acid solutions specifically designed for neonates have been produced. Most, however, do not contain taurine, one of the amino acids present in human milk.

Taurine is an amino acid containing sulphur, which is one of the most abundant amino acids present in mammals.[1] It is found in high concentrations in human milk, being second only to glutamate in concentration in the free amino acid pool of human milk.[2] Until recently little was known about its function apart from its role in the conjugation of bile acids in the liver and its appearance as an end product of methionine and cysteine metabolism. More recent studies have pointed towards a physiological and pharmacological role for taurine in retinal and nervous tissues.[1] There is now increasing evidence to suggest that taurine may be a conditionally essential amino acid—that is, a compound that is not essential for healthy people but which is required by sick people or immature infants.[3]

In a study of patients on long term parenteral nutrition with no taurine supplementation, Geggel *et al* found abnormal electroretinograms in the children examined.[4] Addition of taurine to the parenteral nutrition solution restored the plasma taurine concentrations and the electroretinograms to normal. Plasma taurine concentrations fall rapidly in premature infants when parenteral nutrition without taurine supplementation is given.[5]

Vaminolact (KabiVitrum, sold as Vamin Infant in the United Kingdom) contains taurine 300 mg/l, which is based on the content of taurine in human milk (table 1).

This study was designed to evaluate the suitability of Vaminolact as an amino acid solution containing taurine for the newborn receiving total parenteral nutrition. The efficacy was judged by monitoring plasma amino acid patterns (with particular reference to taurine), growth patterns, and nitrogen balance. The safety of the solution was monitored by measuring acid-base balance and plasma amino acid chromatograms as well as full blood counts and liver and kidney function during the course of treatment. Plasma amino acid concentrations, weight gain, nitrogen balance, and acid-base balance were compared with those of a group of newborns receiving total parenteral nutrition with a different amino acid solution, Vamin glucose (KabiVitrum) (table 1), which was the solution previously used in the neonatal intensive care unit.

Patients and methods

Twenty five consecutively newborn babies who were considered to require parenteral nutrition for a minimum of one week were studied. Informed consent was obtained from the parents in all cases. The treatment group con-

Table 1 Amino acid composition of Vaminolact and Vamin glucose

	Vaminolact (g/l)	*Vamin glucose (g/l)*
Glycine	2·1	2·1
L-Aspartic acid	4·1	4·1
L-Alanine	6·3	3·0
L-Arginine	4·1	3·3
L-Cysteine/cystine	1·0	1·4
L-Glutamic acid	7·1	9·0
L-Histidine	2·1	2·4
L-Isoleucine	3·1	3·9
L-Leucine	7·0	5·3
L-Lysine	5·6	3·9
L-Methionine	1·3	1·9
L-Phenylalanine	2·7	5·5
L-Proline	5·6	8·1
L-Serine	3·8	7·5
L-Threonine	3·6	3·0
L-Tryptophan	1·4	1·0
L-Tyrosine	0·5	0·5
L-Valine	3·6	4·3
Taurine	0·3	0
Total	65·3	70·2

sisted of 15 babies who received Vaminolact as part of their regimen of total parenteral nutrition. The comparison group comprised the previous 10 babies who had received total parenteral nutrition with the same regimen, differing only in the amino acid solution used, which was Vamin glucose.

This investigation was not a randomised trial, as it was considered impossible for practical reasons to prepare and administer two different amino acid solutions in the special care unit at the same time.

A profile of each of the patients, including the indications for total parenteral nutrition, is given in table 2. Mean gestational age, birth weight, and mean age at starting total parenteral nutrition were similar in the two groups of babies (table 2). Apgar scores, maternal age, parity, and problems in pregnancy and labour were also similar between the groups, though duration of membrane rupture was significantly longer in the group receiving Vamin glucose ($p=0\cdot007$).

The first five infants receiving Vaminolact were considered as a 'pilot' group, and had their taurine concentrations measured daily until they were stable on an intake of 2·5 g/kg/day of amino acids. As soon as the taurine concentrations were satisfactory the study continued with the remaining 10 babies. The patients remained in the study until full gastrointestinal feeding had been established. Two of the infants receiving Vaminolact and one receiving Vamin glucose died during the study period, but the deaths were not related to the total parenteral nutrition. All the other infants completed the study.

REGIMEN OF PARENTERAL NUTRITION

The regimen provided carbohydrate, electrolyte, and amino acid solutions as well as lipid emulsion in gradually increasing quantities according to the age of the baby, up to a maximum daily intake of 200 ml/kg of fluid, 2·5 g/kg of amino acid, 4 g/kg of lipid (Intralipid 10%) and a projected maximum caloric intake of 493·2 kJ (118 kcal)/kg/day. Trace elements (Ped-El) water soluble vitamins (Solivito) and fat soluble vitamins (Vitlipid Infant) (all Kabi-Vitrum) were added according to recommended daily requirements. Solutions were given simultaneously by continuous pump infusion into a peripheral vein over a 24 hour period.

Infants were not withdrawn from the study until full enteral feeding was established.

Table 2 Data on newborn infants receiving total parenteral nutrition with Vamin glucose and Vaminolact

Case No	*Gestational age (weeks)*	*Birth weight (g)*	*Age at start (days)*	*Indications for total parenteral nutrition*	*Duration of total parenteral nutrition (days)*
Infants receiving Vamin glucose:					
1	40	2850	3	Necrotising enterocolitis	10
2	31	1530	1	Preterm/respiratory distress syndrome	9
3	29	1290	0	Preterm/respiratory distress syndrome	7
4	31	1460	0	Preterm/respiratory distress syndrome	13
5	30	1870	1	Preterm/respiratory distress syndrome	8
6	41	4000	4	Necrotising enterocolitis	9
7	31	1500	0	Preterm/respiratory distress syndrome	7
8	34	1840	1	Preterm/respiratory distress syndrome	9
9	29	695	1	Preterm/very low birth weight	18
10	29	870	1	Preterm/respiratory distress syndrome	13
Mean (SD)	32·5 (4·5)	1790 (980)	1·2 (1·3)		10 (3)
Infants receiving Vaminolact:					
11	26	740	1	Preterm/respiratory distress syndrome	15
12	26	740	1	Preterm/respiratory distress syndrome	23
13	32	1330	0	Preterm/low birth weight	9
14	29	1280	1	Preterm/congenital heart disease	12
15	40	2720	3	Necrotising enterocolitis	10
16	30	1530	0	Preterm/respiratory distress syndrome	12
17	30	1603	0	Preterm/respiratory distress syndrome	11
18	29	1090	1	Preterm/respiratory distress syndrome	12
19	30	1470	1	Preterm/low birth weight	7
20	25	640	1	Preterm/very low birth weight	11
21	31	1600	1	Preterm/respiratory distress syndrome	10
22	31	1100	1	Preterm/respiratory distress syndrome	23
23	32	1800	1	Preterm/respiratory distress syndrome	9
24	26	920	0	Preterm/respiratory distress syndrome	10
25	29	1550	1	Preterm/respiratory distress syndrome	10
Mean (SD)	29·7 (3·6)	1340 (530)	0·9 (0·7)		12 (5)

MONITORING

Routine monitoring was carried out with full blood counts, liver function tests, and estimations of serum concentrations of urea and electrolytes, glucose, acid-base values, magnesium, phosphorus, and triglycerides. Plasma amino acid analyses were performed before starting the study, after 24 hours of an intake of 2 g/kg of amino acid, and again after three days on an intake of 2·5 g/kg/day of amino acid. They were carried out weekly thereafter. The amino acid concentrations were measured by ion exchange chromatography with a Locarte amino acid analyser. Plasma ammonia concentrations were checked when the infant had been on an amino acid intake of 2·5 g/kg/day for two days.

Urine was collected for estimation of 24 hour nitrogen balance on an amino acid intake of 2 g and 2·5 g/kg/day. Because of difficulties in collecting urine specimens it was not possible to calculate nitrogen balance for all the infants. Samples were analysed for nitrogen content by Tingvall's method.[6] In calculating the nitrogen balance an extra 25% of the urinary nitrogen output was added as an estimate of the faecal nitrogen loss.[7]

Body weight was recorded daily, unless contraindicated by instability of the infant's condition.

STATISTICAL ANALYSIS

The significance of differences in proportions was assessed by Fisher's exact test. All quantitative and ordinal variables were examined by the Wilcoxon two sample test for independent data. A p value of <0·05 was accepted as significant.

Results

PLASMA AMINO ACIDS

Table 3 shows the mean plasma amino acid concentrations in the two groups before starting the infusion of amino acid solution, and on intakes of 2 g/kg/day and 2·5 g/kg/day of amino acids.

Transient hypertyrosinaemia (>196 µmol/l) occurred in four infants, three receiving Vamin glucose and one receiving Vaminolact.[8] In two infants it resolved spontaneously and in the remaining two it resolved after additional vitamin C had been given.

One baby on Vaminolact, who had congenital heart disease and cardiac failure (table 2, case 14), had total parenteral nutrition withheld for 28 hours from day 4 because of a mildly raised glutamine concentration (1032 µmol/l).

There were no other abnormalities in amino acid concentrations that necessitated treatment or change in the total parenteral nutrition regimen.

TAURINE CONCENTRATIONS

In both groups of infants the taurine concentrations were lower on an amino acid intake of 2 g/kg/day than before the infusion, but the concentrations rose again when the intake was increased to 2·5 g/kg/day (fig 1). Compared with the group receiving Vamin glucose the mean taurine concentration before infusion was lower in the group receiving Vaminolact, but the

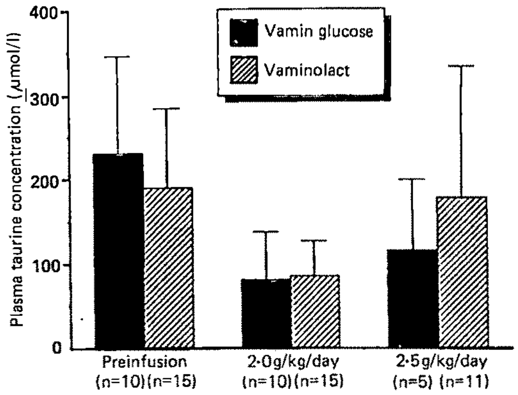

Figure 1 Mean (SD) plasma taurine concentrations before treatment, and during infusions of 2·0 g/kg/day, and 2·5 g/kg/day.

Table 3 Mean (SD) plasma amino acid concentrations (µmol/l)

	Before infusion		*Projected amino acid intake*			
	Vamin glucose	*Vaminolact*	*2·0 g/kg/day*		*2·5 g/kg/day*	
			Vamin glucose	*Vaminolact*	*Vamin glucose*	*Vaminolact*
Actual amino acid intake (g/kg/day)	Not applicable	Not applicable	1·9+0·1	1·8+0·2	2·3+0·1	2·3+0·2
Taurine	230 (117)	190 (95)	79 (58)	85 (43)	114 (84)	177 (156)
Aspartic acid	19 (11)	22 (13)	34 (28)	30 (20)	31 (31)	43 (44)
Threonine	145 (79)	144 (86)	162 (50)	244 (91)***	152 (41)	310 (122)**
Serine	111 (27)	110 (38)	221 (69)	179 (61)	211 (38)	235 (84)
Glutamine	225 (86)	436 (231)***	312 (170)	492 (216)	329 (141)	480 (126)
Glutamic acid	85 (76)	51 (39)	136 (157)	41 (38)	159 (111)	22 (34)**
Glycine	261 (86)	290 (129)	305 (74)	277 (98)	292 (84)	387 (76)
Alanine	214 (67)	204 (85)	257 (175)	202 (61)	233 (101)	326 (126)
Valine	76 (15)	115 (56)*	156 (32)	149 (39)	180 (17)	181 (58)
Cystine	25 (8)	44 (15)***	45 (15)	56 (15)	43 (13)	79 (28)**
Methionine	41 (15)	39 (13)	46 (16)	42 (13)	58 (19)	50 (20)
Isoleucine	40 (9)	56 (17)***	76 (21)	70 (18)	91 (17)	86 (38)
Leucine	69 (15)	68 (19)	122 (26)	133 (41)	115 (22)	166 (56)
Tyrosine	118 (71)	94 (38)	296 (323)	81 (101)***	116 (61)	51 (31)**
Phenylalanine	72 (19)	75 (33)	143 (51)	78 (28)***	147 (41)	98 (53)
Lysine	159 (62)	144 (52)	200 (74)	223 (97)	131 (59)	253 (63)***
Ornithine	62 (33)	48 (20)	83 (42)	83 (39)	53 (20)	97 (43)
Histidine	123 (34)	115 (28)	142 (29)	135 (31)	142 (39)	138 (28)
Tryptophan	37 (13)	40 (24)	48 (29)	62 (42)	38 (8)	62 (41)
Arginine	25 (27)	37 (24)	35 (27)	63 (59)	40 (11)	48 (47)

Vamin glucose compared with Vaminolact: *p<0·05, **p<0·02, and ***p<0·01.

mean concentrations on infusions of 2 g and 2·5 g were higher in the group receiving Vaminolact though this difference was not significant.

Taurine concentrations exceeded the upper limit of the reference range (256 μmol/l, suggested by Clayton *et al*[8]) in two babies who were receiving Vaminolact. Both were extremely ill at the time, one with congenital heart disease and cardiac failure and the other with sepsis and intraventricular haemorrhage (table 2, cases 14 and 20), and both died soon afterwards, the deaths being unrelated to total parenteral nutrition. In both cases the concentrations of other amino acids were also raised.

Taurine concentrations measured daily on the first five babies receiving Vaminolact were all satisfactory except in the case of case 14 in whom it was mildly increased on two occasions (fig 2).

OTHER BIOCHEMICAL DATA

Several babies in each group had raised creatinine concentrations. This was not unexpected as these infants all had patent ductus arteriosus and fluids were being restricted.

One infant in each group had a mildly raised plasma ammonia concentration (<140 μmol/l). As both infants had started (the following day) enteral feeds by the time the result was reported, however, no alteration was made in the total parenteral nutrition regimen.

There were no abnormalities in liver function tests. Serum proteins were low in many cases, but this is expected in sick premature infants.

Six babies receiving Vaminolact and three receiving Vamin glucose developed metabolic acidosis. In the case of five babies (two receiving Vaminolact and three receiving Vamin glucose) the acidosis was unexplained by sepsis but the episode was brief in all cases and responded to treatment with bicarbonate. Some small babies needed daily maintenance doses of bicarbonate. In some babies the total parenteral nutrition regimen was altered. In the group receiving Vaminolact the amino acid solution was stopped for one baby for 24 hours, and for three days for the baby who subsequently died of sepsis. In the group receiving Vamin glucose the solution was stopped for a few hours of one infant, and for another infant it was decided not to increase the intake of amino acids to 2·5 g/kg/day because of acidosis. In one receiving Vaminolact the acidosis was accompanied by mild increases in threonine, isoleucine, and leucine concentrations.

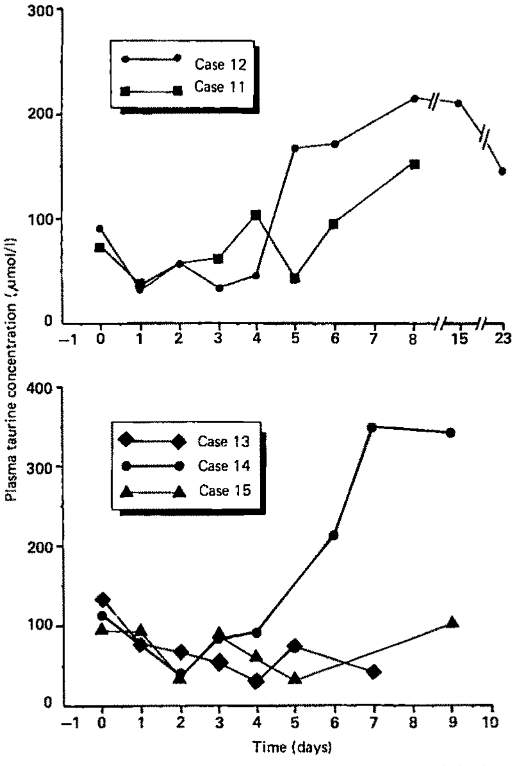

Figure 2 Plasma taurine concentrations before and during infusion of Vaminolact in cases 11, 12, 13, 14, and 15 (pilot group).

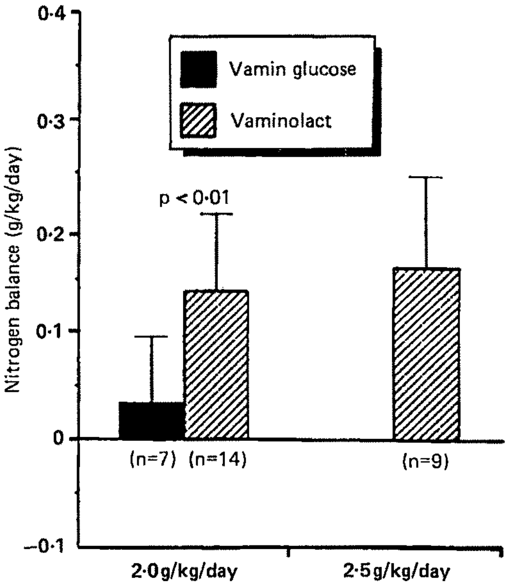

Figure 3 Mean (SD) nitrogen balances during infusions of 2·0 g/kg/day and 2·5 g/kg/day.

NITROGEN BALANCE

The mean nitrogen balance on amino acid intakes of 2 g and 2·5 g/kg/day for the two groups of infants are shown in fig 3. Nitrogen retention on an intake of 2 g/kg/day was significantly higher among those receiving Vaminolact, but no such comparison could be made on the higher intake as nitrogen balance was estimated in only one infant receiving Vamin glucose.

BODY WEIGHT

Most infants lost weight within the first few days, and in many cases this weight loss was compounded by fluid restriction which was instituted because of patent ductus arteriosus. Of the 15 subjects receiving Vaminolact, five regained their birth weight by day 7 to 11 while on total parenteral nutrition. Four babies receiving Vamin glucose regained their birth weight by day 4 to 17 on total parenteral nutrition.

Discussion

The purpose of this study was to assess the efficacy and safety of Vaminolact as an amino acid solution containing taurine for use in neonates. Studies of low birthweight infants who have been fed a variety of formulas with and without taurine support the indication that there is a dietary requirement for taurine in rapidly growing infants.[9 10] The main pathway for the biosynthesis of taurine is through methionine, cysteine, cysteine sulphinic acid, and hypotaurine.[11] This pathway does not seem to become fully active until some time after full term. Cystathionase is absent during fetal development.[10] In human tissues, particularly those of neonates, only trace amounts of cysteine sulphinic acid decarboxylase are present.[1]

Although this study was not randomised, the groups were comparable for all the variables examined except duration of membrane rupture.

No serious abnormalities in amino acid concentrations were observed. Bearing in mind the short term nature of the study, the plasma taurine concentrations attained on Vaminolact were encouraging. After an initial fall from the value before infusion, the taurine concentration showed a more rapid recovery after infusion of Vaminolact than of Vamin glucose, although this difference was not significant. Follow up of one patient who required more prolonged total parenteral nutrition indicated a levelling out of the taurine concentration at an acceptable and non-toxic level. Griffin and Gray in their study of Vaminolac (Vaminolact without taurine), also showed this fall followed by a rise in taurine concentration.[12] The mean taurine concentration reached on an amino acid intake of 2·5 g/kg/day in their study was lower than in the group receiving taurine supplementation of the present study.

Phenylalanine concentrations were within the reference range with Vaminolact and were lower than in the Vamin glucose group. Neither group of subjects developed the hyperphenylalaninaemia that has recently been a cause of concern in parenterally fed newborns.[13]

One baby (of 31 weeks' gestation) had a raised tyrosine concentration that resolved spontaneously. In the control group three infants whose gestational age at birth ranged from 29 to 31 weeks developed raised tyrosine concentrations. Dickinson *et al* in their study of low birthweight newborn babies, found raised tyrosine concentrations in many babies, and discussed the association of tyrosinaemia with developmental immaturity.[14]

Recent studies have suggested that taurine deficiency may be associated with the development of cholestasis in experimental animals, and one study of three children on total parenteral nutrition without taurine supports the theory that taurine deficiency produces cholestasis in humans, and is possibly associated with the development of the severe hepatic dysfunction that sometimes develops on patients receiving total parenteral nutrition.[15] Liver function tests were satisfactory in both groups in this study, but a longer study period would be necessary to investigate the effect of taurine supplementation in the prevention of hepatic dysfunction associated with total parenteral nutrition.

Nitrogen balance where assessed was predominantly positive, and there was greater nitrogen retention in infants given Vaminolact than in those given Vamin glucose.

In many cases, energy intake was lower than intended and weight gain was less than predicted. In most of them this was the result of the necessity to restrict fluids in patients with patent ductus arteriosus, or because of delay in starting Intralipid because of jaundice of prematurity. Several babies had regained their birth weight, and most showed a positive trend in this direction before the end of the study period.

We found Vaminolact to be a safe and effective amino acid solution for use in critically ill, but stable, babies. Any problem that we did encounter, as outlined above, would not be unexpected in a group of small and sick infants such as those in the study. There remains the need for extreme vigilance when using total parenteral nutrition in neonates, however, not only with regard to taurine, but also to tyrosine and phenylalanine, so frequent monitoring is essential. Ill septic infants have a reduced ability to clear amino acids and particular care must be taken in this group when these solutions are being given.

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Pulmonary intravascular lipid in neonatal necropsy specimens

J W L Puntis, D I Rushton

Abstract

The lungs of 482 liveborn infants were examined at necropsy for the presence of intravascular lipid. Forty one patients had received parenteral feeding (including lipid emulsion in 30), and 441 had died before starting feeds or had received enteral feeds alone. Tissue was processed into wax and then stained with Sudan black; intravascular lipid was found in 15 of 30 infants who had received intravenous fat (Intralipid), but in no others. Those patients with positive lipid staining had received significantly more fat during parenteral nutrition than those in whom intravascular lipid was not found but the two groups were otherwise clinically indistinguishable. Using this staining technique intravascular lipid can be shown relatively often, although only in patients who have received intravenous lipid emulsion. The location of fat, predominantly in small pulmonary capillaries, and the absence of lipid emboli in other organs, suggests that lipid coalescence takes place before death and is not a postmortem artefact. The clinical relevance remains uncertain.

Although the occlusion of pulmonary capillaries by intravascular fat has been reported in necropsy specimens of newborn infants who were given parenteral nutrition[1] the incidence, aetiology, and clinical importance of this are controversial. In one study, lung tissue containing intravascular lipid was found to be rich in linoleic acid,[2] consistent with the lipid 'emboli' having been derived from the intravenous fat emulsion used during parenteral nutrition. Other workers have suggested that intravascular lipid is no more than postmortem artefact.[3] The aims of this study, therefore, were to determine prospectively the incidence of pulmonary intravascular fat at necropsy in both enterally and parenterally fed infants, and to examine its association with parenteral feeding.

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Patients and methods

INFANTS RECEIVING PARENTERAL NUTRITION

In a regional neonatal intensive care unit during a 10 year period (1980–9) 41 infants who had been parenterally fed came to necropsy. Their median (range) gestational age was 28 weeks (25–40) and weight 880 g (450–2820). The most common indication for parenteral nutrition was prematurity and failure to tolerate enteral feeding in association with severe hyaline membrane disease requiring ventilation (n=38); indications in the three remaining patients were necrotising enterocolitis, ischaemic colitis, and ileal atresia. All patients received amino acid/dextrose solution (Vamin 9 glucose, KabiVitrum) and 30 had also been given an intravenous fat emulsion (Intralipid 10%, KabiVitrum). Routine biochemical monitoring of fat metabolism was not carried out other than for daily visual inspection of plasma for lipaemia. Lipid infusion rates varied between 0·5 g/kg/day and 3·0 g/kg/day, and the infusions were discontinued each morning four hours before blood sampling. Details of feed intake and clinical condition were obtained retrospectively from nursing and medical records.

INFANTS RECEIVING ENTERAL NUTRITION

In addition to those who had been parenterally fed, the lungs from 441 other live born infants were also studied for evidence of intravascular pulmonary fat. These patients had either been fed by the enteral route alone, or had died before any form of feeding was started.

PREPARATION OF TISSUE SPECIMENS

Necropsy specimens were prepared according to a standard procedure. One block of tissue was taken from each lobe of each lung and processed in wax using chloroform to remove neutral fat. Sections were then stained with Sudan black and examined for residual lipid. All specimens were examined by the same person (DIR) who did not know whether the parenterally fed infants had received Intralipid, or the amino acid/dextrose solution alone. Organs other than lungs were not routinely stained for fat by this method.

STATISTICAL ANALYSIS

Significance of differences were assessed by the Mann-Whitney U test or the χ^2 test, and a probability of $<0·05$ was accepted as significant.

Results

INFANTS RECEIVING PARENTERAL NUTRITION

For the group as a whole, the median (range) duration of parenteral nutrition was 14 days (1–46). Pulmonary intravascular lipid was not found in any of the 11 patients given amino acid/dextrose mixtures alone, but was present in 15 (50%) of infants who had received Intralipid. Lipaemic serum had not been noted in any patients during feeding. In all cases, lipid was found in the pulmonary capillaries, usually towards the periphery of lobules, and in two

Patients receiving intravenous fat emulsion: comparison at time of death between those with and without pulmonary intravascular lipid in necropsy specimens. Values are expressed as median (range)

	Pulmonary intravascular lipid in necropsy specimens		
	Present (n=15)	*Absent (n=15)*	*p Value*
Weight (g)	880 (530–1880)	840 (450–2820)	0·88
Postconceptual age (weeks)	27 (25–34)	28 (26–38)	0·33
Age at death (days)	28 (8–54)	19 (4–84)	0·06
No of days that fat was infused	16 (1–35)	4 (1–28)	0·003
Total amount of fat given (g/kg body weight)	36 (11–112)	5·5 (1–49)	<0·0001
Interval between death and necropsy (hours)	58 (9–120)	68 (27–120)	0·77

of these lipid was also found in alveolar macrophages. One patient was strikingly different in that lipid was found in pulmonary arterioles; myocardial, pancreatic, brain stem, and salivary gland capillaries; renal glomerular and medullary vessels; and the portal vein.

Ten of 15 patients who had lipid in their lungs and 12 of those who did not had received Intralipid infusions within 24 hours of death (p=0·88). Four patients with positive intravascular fat staining had not been given Intralipid for between three and eight days before death. The clinical characteristics of the patients who received Intralipid are shown in the table. Patients in each category were similar except in respect of the amount of Intralipid received, which was significantly greater among those who had positive intravascular fat staining at necropsy.

From review of the clinical records it did not seem that alteration in the rate of lipid infusion was associated with subsequent deterioration in the clinical condition in any of the patients, although we did not analyse blood gas and ventilation data in relation to lipid infusion. Heparin was not included in feeding solutions but all patients received 3 units of heparin each hour with arterial flush solutions during part or all of the time they were receiving parenteral nutrition. There were identical proportions of small for gestational age infants among those in whom intravascular fat was and was not found.

INFANTS RECEIVING ENTERAL NUTRITION

None of the 441 infants who received enteral nutrition, or died before feeding could be started, had evidence of intravascular fat at necropsy.

Discussion

We have confirmed the previously described association between the giving of Intralipid and the presence of pulmonary lipid emboli at necropsy, using wax impregnation and Sudan black staining of lung tissue. Although we found intravascular fat exclusively in patients who had been given intravenous lipid emulsion (half), some studies using alternative tissue preparation and staining methods have shown occasional incidences of intravascular fat in patients who had not received Intralipid.[4] [5] This discrepancy probably relates to the different techniques used for diagnosing the presence of lipid. Processing tissue into wax removes neutral lipid so that fat that is seen after subsequent staining with Sudan black must be in a form that is relatively insoluble in chloroform. That this fat is Intralipid seems in little doubt[2]; its vegetable origin and coating of egg phospholipid possibly make it less soluble than endogenous fat. Intravascular fat seen with Oil Red O in frozen sections of lungs from patients who have not received Intralipid may on the other hand be of endogenous origin, and this is probably a phenomenon quite different from the lipid emboli seen after parenteral nutrition. In one study that challenged the association between Intralipid and fat emboli lungs were fixed immediately after death and then stained with Sudan IV.[3] This method has not been used by other workers and is less likely to show up Intralipid, as Sudan IV is not as lipid soluble as Sudan black.

Patients with intravascular lipid at necropsy had received significantly greater amounts of fat than those without (p<0·0001), which adds further support to the existence of a relationship between the use of Intralipid and the presence of fat emboli at necropsy. Lipid was infused at rates regarded as being metabolically well tolerated (<3 g/kg/day).[6] We cannot comment on differences in lipid metabolism between the two groups as no monitoring other than inspection of the plasma for lipaemia was done, and no instances of lipaemia were recorded. Visual inspection of plasma is, however, an unreliable way of predicting lipid profiles.[7] We did not observe lipid deposits in pulmonary arterial walls as some workers have described, although we have seen similar lesions in other patients who had received parenteral nutrition for many months.[8]

Heparin given through arterial catheters could possibly affect lipid clearance by increasing the amount of lipases in the circulation[9]; a standard concentration of heparin was used in arterial flush solutions, however, and intake in patients with and without intravascular fat was much the same. Although infants who are small for gestational age may clear lipid from the circulation more slowly than appropriately grown infants, there was no difference in the proportion of growth retarded patients with and without positive fat staining.[10]

The observation that lipid is usually limited to small pulmonary capillaries and not found throughout the entire vascular system suggests a filtering out process taking place before cessation of circulation. The assertion that intravascular lipid is merely a postmortem artefact would therefore seem implausible, although this could apply to our one patient with lipid seen in many different organs. Because most Intralipid droplets are of similar size to endogenous chylomicrons (mean diameter 0·15 μm), before emboli can lodge in the pulmonary capillaries (8–12 micron diameter) the droplets must coalesce for some reason. Coalescence or 'creaming' of Intralipid occurs in vitro in the presence of C reactive protein,[11] and fat embolism has been described in one infant with a high plasma concentration of C reactive protein.[12] Many preterm infants die of multisystem failure, sometimes with infection as an additional complication, and it is probable that C reactive protein concentrations are often raised.[13] Recent evidence, however, casts doubt on the relationship between creaming and C reactive protein concentrations.[14]

As lipid emboli were found in some patients who had not received any Intralipid for several days before death (over a week in two cases), it is possible that once emboli have formed they may remain relatively resistant to degradation. Although there is little evidence to suggest that fat microembolisation in itself is harmful to the patient,[15] under certain circumstances high infusion rates of lipid have been associated with falls in arterial oxygen saturation.[16] Whereas it is tempting to think that this may be caused by lipid microemboli blocking pulmonary capillaries and thereby altering perfusion ventilation ratios, there is evidence that an alternative mechanism exists through which fat leads to increases in concentrations of vasodilating prostaglandins that unblock hypoxic vasoconstriction and thereby increase intrapulmonary right to left shunting.[17] In none of our patients was any such clinical effect commented on in the medical records.

Our data suggest that lipid microemboli may be common during administration of intravenous lipid emulsion but are probably of little clinical relevance. Caution in the use of Intralipid is advisable in those infants at risk of increased pulmonary vascular resistance,[18] but anxiety about lipid emboli should not preclude the use of lipid emulsions in preterm infants who cannot tolerate enteral feeding.

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Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessment after five years of screening

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Abstract

Screening of the newborn for cystic fibrosis by measurement of immunoreactive trypsin has been undertaken on alternate weeks in Wales and the West Midlands for five years since 1985 to evaluate the possible clinical benefits of early diagnosis. Patients detected by screening and those diagnosed by clinical symptoms alone were assessed annually for differences in clinical, anthropometric, and biochemical variables. Fifty eight infants not considered to be at risk of cystic fibrosis (they did not present with meconium ileus and do not have a sibling with cystic fibrosis) have been detected by screening and they have been compared with 44 children who were diagnosed clinically. This latter group includes nine children whose screening was negative but who were recognised subsequently to have cystic fibrosis. The mean age at diagnosis of the screened group was significantly lower than that of the group diagnosed clinically. Excluding admissions for diagnostic tests for cystic fibrosis, the screened group spent a significantly shorter time in hospital during the first year of life. The results of all other comparisons made between the screened group and those diagnosed clinically were similar up to the age of 4 years.

Screening for cystic fibrosis by measurement of the concentration of immunoreactive trypsin in the blood has now been done for 10 years, since Crossley *et al* first described the phenomenon of raised immunoreactive trypsin values in heel-prick blood samples from neonates with cystic fibrosis.[1 2] Reasons for screening for cystic fibrosis (or any other disease) rest upon the principles of Wilson and Jungner.[3] In essence, the disease should have a latent or early symptomatic state that can be modified by agreed treatment. While the former is usually true for cystic fibrosis, there is at present no agreed treatment protocol.[4]

Several groups have attempted to substantiate the case for screening for cystic fibrosis by making longitudinal comparisons of screened patients and those recognised in previous years by clinical criteria.[5–8] Other reports have concerned the better clinical state of children with cystic fibrosis who were diagnosed during the first year of life—earlier than contemporaries[9] or siblings.[10] All these studies have been open to the criticism that like has not been compared with like.[11] The diagnostic delay that occurs in cystic fibrosis can, however, be improved by screening,[12] and the identification of nutritional deficiencies by screening in some infants with cystic fibrosis before the age of 2 months gives further support for screening and early diagnosis.[13]

To find out the possible clinical benefits of early diagnosis after screening, a large comparative study of screening for cystic fibrosis by measurement of immunoreactive trypsin on routinely collected blood spots (Guthrie card specimens at 5–10 days of age) was set up in Wales and the West Midlands in January 1985, funded by the Cystic Fibrosis Research Trust. During the five year period 227 183 neonates were screened for cystic fibrosis (table 1) and an estimated 246 959 were not screened (table 2). In this paper we make a clinical comparison between screened and clinically diagnosed patients from data produced to December 1989.

Patients and methods

IDENTIFICATION OF PATIENTS

The protocol of the trial has been described previously.[11] Infants born in Wales (population 2·7 million) and the West Midlands (population 4·1 million) were tested on alternate weeks, thus identifying two groups in each area: screened and unscreened. Results for patients in both areas are considered together.

Specimens from neonates collected in central Birmingham were sent to a separate local screening laboratory and no children born in the central Birmingham area are included in this

Table 1 Details of infants screened 1985–9. Total number of specimens received: 227 183

	No of specimens	
Positive first immunoreactive trypsin test	947 (0·42%)	
Positive second immunoreactive trypsin test	98	
False positive tests (sweat test negative)	33	
Infants identified as having cystic fibrosis (sweat test positive):	65	
Not at risk		58
With meconium ileus		3
With elder sibling with cystic fibrosis		4
Specimens giving false negative diagnoses for cystic fibrosis:	13	
Not at risk		9
With meconium ileus		3
With elder sibling with cystic fibrosis		1
Total No of cases of cystic fibrosis diagnosed by screening	78 (1/2912)	

Table 2 Details of infants who were not screened 1985–9

Estimated No of unscreened infants	246 959	
Total No of unscreened infants known to have cystic fibrosis:	66 (1/3741)	
Not at risk		35
With meconium ileus		19
With elder sibling with cystic fibrosis		12

trial. As the Birmingham Children's Hospital is in central Birmingham, and most infants born in the West Midlands with meconium ileus are referred there, there is an abnormally high incidence of children with meconium ileus in the unscreened group of patients. This anomaly does not, however, affect the random allocation of children who were not at risk into the 'screened' and 'clinical' groups at the annual assessment.

Permission for the trial was obtained from the ethics committee of each area health authority. A change in attitude to the protocol in one district of the West Midlands led to stopping the screening early in the West Midlands (in October 1989), though screening continued in Wales until December 1989. Patients with cystic fibrosis born in the West Midlands between October and December 1989 are included in the unscreened group. We feel that three months out of a five year period is unlikely to have a significant effect on the random allocation of children into screened and unscreened groups.

Immunoreactive trypsin was measured at 5–10 days by radioimmunoassay using the Behring kit (Hoechst Pharmaceuticals).[11] Subjects with a positive immunoreactive trypsin result (over 900 ng/ml) were retested at 6 to 8 weeks. As immunoreactive trypsin in infants with cystic fibrosis falls with time,[1 11] the upper limit of normal for the second test was taken as 600 ng/ml and if this was exceeded the child was referred by the general practitioner to the local paediatrician for sweat testing by pilocarpine iontophoresis.[14] No follow up was arranged for infants with only a single positive immunoreactive trypsin value, or for those with two positive results followed by a normal sweat test. Routine treatment included chest physiotherapy, antibiotics according to an agreed protocol, pancreatic enzymes according to clinical need, and vitamin supplementation.

FOLLOW UP OF PATIENTS

Children were assessed on entry to the trial, and various groups were identified based on mode of presentation.

Yearly comparisons were made between infants identified after positive immunoreactive trypsin screening and those diagnosed clinically (the latter group includes those with a false negative immunoreactive trypsin result who were later found to have cystic fibrosis). Infants with meconium ileus and siblings of known patients with cystic fibrosis were considered to be 'at risk' of cystic fibrosis and their results have been excluded from the yearly comparisons.

Each child was reviewed annually by one of us. Detailed information was obtained about the child's health during the previous year including admissions to hospital for illnesses that could be related to cystic fibrosis. A full clinical examination and chest radiograph were done, and height, weight, and skinfold thickness were measured. A blood sample was obtained for various indices: haematological (full blood count, clotting picture, ferritin and folate concentrations); biochemical (plasma electrolyte concentrations, liver function tests, and concentrations of fat soluble vitamins, cholesterol, fatty acids, trace elements, uric acid, and immunoreactive trypsin); immunological (concentrations of immunoglobulins); and for virus titres.

Between annual assessments children were followed up by their local paediatricians.

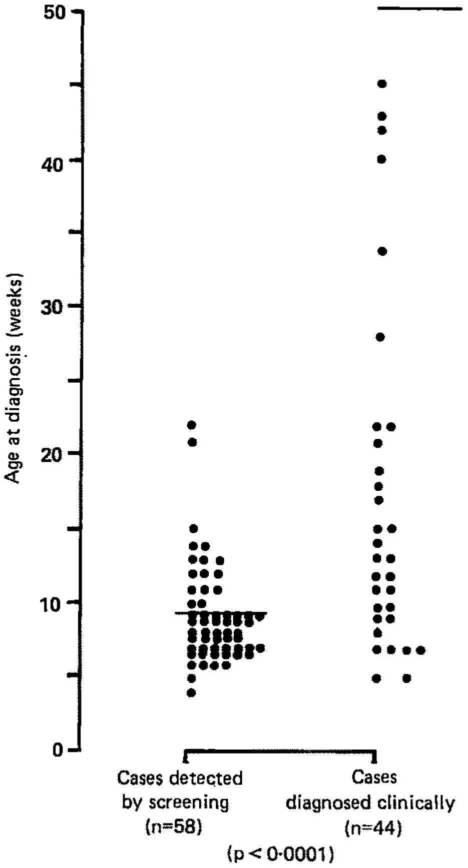
STATISTICAL ANALYSIS

The distribution of many of the variables was skewed, and consequently comparison of the data is by the non-parametric Mann-Whitney U test.

Results

DETECTION OF INFANTS WITH CYSTIC FIBROSIS

Between January 1985 and December 1989, 227 183 specimens collected in Wales and the West Midlands were routinely screened, and 65 infants with cystic fibrosis were detected after positive screening, of whom 58 were considered not to be 'at risk' (table 1). In addition, 13 specimens from infants subsequently proved to have cystic fibrosis were negative by immunoreactive trypsin screening. Thus there is a total of 78 infants known to have cystic fibrosis in this group giving an incidence of 1/2912. During the same period within the same area an estimated 246 959 specimens were not screened and 66 infants with cystic fibrosis were detected, although only 35 were not 'at risk' (table 2). The



Ages of children at diagnosis; the horizontal bars represent the means. The ages (weeks) of children over the age of 1 year at diagnosis were 71, 80, 87, 95, 116, 119, 123, 150, 151, 156, 213, and 230.

Table 3 Symptoms in infants not considered to be at risk of cystic fibrosis but detected by screening compared with those detected clinically. Figures are expressed as numbers (%)

	Infants detected by screening (n=58)	*Infants detected clinically (n=44)*
Respiratory symptoms only	10 (17)	4 (9)
Gastrointestinal symptoms only	9 (16)	7 (16)
Respiratory and gastrointestinal symptoms	17 (29)	33 (75)
Failure to thrive only	6 (10)	0
Asymptomatic	16 (28)	0

difference between the total numbers of patients with cystic fibrosis in each group (78 and 66) was not significant ($\chi^2=2\cdot27$, df=1, $0\cdot2>p<0\cdot1$), but there was a significant difference between the numbers of infants with cystic fibrosis not 'at risk' (58 and 35) ($\chi^2=7\cdot78$, df=1, $p<0\cdot01$).

ASSESSMENT AT ENTRY

Information at entry into the trial is available on all patients. Infants presenting with meconium ileus and siblings of patients known to have cystic fibrosis have been excluded. Nine children with false negative screening results are included in the group that was diagnosed clinically.

The mean (SD) age at diagnosis of the screened patients (9·1 (3·1) weeks) was significantly lower than that of those clinically diagnosed (50·7 (60·5) weeks) ($p<0\cdot001$, figure).

Symptoms at diagnosis are shown in table 3. Less than one third of the screened group was asymptomatic at the time of diagnosis, while the others had symptoms referrable to the respiratory or gastrointestinal systems, or both. Three quarters of the group diagnosed clinically had both respiratory and gastrointestinal symptoms at the time of diagnosis.

Information about hospital admissions with symptoms attributable to cystic fibrosis before the time of diagnosis was available in most cases. In the screened group, 11 of 55 patients had had one such admission, and in only one case was the diagnosis of cystic fibrosis being considered before notification of the positive screening test result. Twenty six of 43 children clinically diagnosed had had at least one such admission.

ANNUAL ASSESSMENT

The number of children assessed in each of the first four years of life is shown in table 4. Clinical comparisons were made between infants detected by screening who had no risk factors for cystic fibrosis and children who were diagnosed clinically.

There were no significant differences in weight and height SD scores between the two groups at any age, though there was a tendency for the scores to improve in both groups from the ages of 1–3 years (table 5).

Shwachman scores (score for overall well being; points deducted for adverse features; maximum score 100)[15] and Chrispin-Norman scores (chest radiography only; points allocated for adverse features to a total of 38)[16] were similar at the ages of 1 to 4 years. The mean Shwachman scores were between 85 and 90 in both groups and the mean Chrispin-Norman scores between 4 and 7 at all ages.

Table 4 No of infants assessed at ages 1–4 years

	Age (years)			
	1	*2*	*3*	*4*
No detected by screening	44	33	23	12
No detected clinically	22	21	13	7

Table 5 Mean (SD) weight and height SD scores for those patients detected by screening and those diagnosed clinically at ages 1–4 years. There was no significant difference at any age

	Patients detected by screening	*Patients detected clinically*
Weight SD scores:		
1 year	−0·62 (1)	−0·54 (0·9)
2 years	−0·38 (0·8)	−0·47 (0·9)
3 years	−0·12 (1)	−0·4 (0·4)
4 years	−0·4 (1·2)	−0·15 (0·4)
Height SD scores:		
1 year	−0·67 (1·1)	−0·55 (1)
2 years	−0·47 (0·9)	−0·77 (0·9)
3 years	+0·07 (1)	−0·35 (0·9)
4 years	−0·09 (1·2)	−0·39 (0·9)

There were no significant differences between the groups in the results of any of the laboratory tests.

During the first year of life only, the mean (SD) number of hospital admissions (screened 1·3 (1·9), clinical 3·2 (2·7) admissions) and length of time spent in hospital with illness associated with cystic fibrosis (screened 19·2 (42·9) days, clinical 27 (22·7) days) were significantly greater in the group diagnosed clinically ($p<0\cdot01$). Admissions for diagnosis and initiation of treatment have been excluded from these figures.

DEATHS

There have been four deaths so far, all in the group diagnosed clinically. One infant who had presented with meconium ileus and had a positive sweat test, died at the age of 10 weeks of sudden infant death syndrome. Another child with a chest infection who had been confirmed to have cystic fibrosis by two positive sweat tests died at the age of 11 weeks. A third infant with extensive chest infection and a positive sweat test also died at the age of 11 weeks, despite ventilation. A fourth child, who had been treated for asthma, died suddenly at the age of 22 months; at necropsy cardiomyopathy and features of cystic fibrosis were found. No sweat test had been done though it transpired later that this child had had two first cousins with cystic fibrosis. A retrospective immunoreactive trypsin analysis of the neonatal blood sample of the third and fourth patients showed positive results in both cases.

Discussion

This large screening study carried out in Wales and the West Midlands over a five year period has shown that neonatal screening for cystic fibrosis could be integrated into the existing national screening programme. Values for specificity and reliability of the immunoreactive trypsin test were similar to those found previously.[17]

The incidence of cystic fibrosis in the screened population (1/2912) was slightly lower than previously reported,[18] but this figure may have been affected by the exclusion of children born in the West Midlands who had meconium ileus. When the incidence is calculated for Welsh children alone (where this anomaly does not occur) the figure is 1/2671. It is possible that this incidence will increase if more children with negative immunoreactive trypsin tests are found to have cystic fibrosis.

The false negative incidence in this study, at 12·8%, is higher than in some previous reports,[17][19] but lower than in another.[20] The incidence would not be reduced by lowering the cut off value for the initial immunoreactive trypsin test. In our opinion the immunoreactive trypsin test is not as specific as previously reported[1] and it is important to stress the need for sweat testing where cystic fibrosis is suspected clinically.

The incidence of false positive results in the study is similar to that found by others.[5] The period between the initial positive immunoreactive trypsin test and the result of the sweat test is distressing to families and it is essential to keep this time to a minimum. A survey of some of the families who took part in this study showed that most parents supported screening, whether their child had been screened or clinically diagnosed.[21] All families experienced some change in their feelings for their child after learning the diagnosis, however, and 'several families emphasised the importance of minimal delay between the initial mention of the possibility of cystic fibrosis on immunoreactive trypsin testing and the confirmation (or otherwise) of the diagnosis'.

The identification of the cystic fibrosis gene and major deletion (δ F508) found in about 70% of cystic fibrosis chromosomes of northern European origin could permit rapid diagnosis of about half the patients who develop cystic fibrosis without a previous family history, who are homozygous for this deletion.[22] The obligatory false negative rate of the other half implies that neonatal screening for cystic fibrosis by DNA analysis is not appropriate at present.

During the five years of the study 144 children with cystic fibrosis have entered the trial. Of these, 78 were screened and 66 not screened. When children 'at risk' of cystic fibrosis are excluded there are significantly fewer children in the unscreened group (35 compared with 58 screened). This indicates a possible cohort of children in the unscreened population who have cystic fibrosis who have not yet been diagnosed, and lends support to the theory of Warwick that a substantial number of patients with cystic fibrosis remain undiagnosed, some for years, and some even at necropsy.[23]

Analysis of the 'not at risk' groups (screened and clinically diagnosed) permits a comparison of early and late diagnoses and an assessment of the effects of screening. A significant difference is found for age at diagnosis (figure). The SD is wide for the clinical group with 27% over the age of 1 year, the oldest being 4·5 years, which is similar to results reported previously for unscreened patients.[12]

Most children who are detected by screening had symptoms attributable to cystic fibrosis at the time of diagnosis and several had already been admitted to hospital. Cystic fibrosis was not considered in some of the clinically diagnosed group until they had had more than one admission to hospital; this has also been reported by Wilcken *et al.*[12]

Although the screened patients were diagnosed and treated earlier, we were unable to show any clinical differences between the two groups of patients at the ages of 1 to 4 years. Previous studies have shown differences among older children and it is possible the patient groups will diverge later.[7][8] The present tests may be too insensitive to detect any differences that are present. Our patients are too young to do lung function tests; when this is possible these tests may allow finer discrimination of differences between those who were screened and those who were diagnosed clinically.

We did find that the screened children had significantly fewer admissions to, and spent less time in, hospital in the first year of life for problems related to cystic fibrosis, even when admissions for diagnosis and initiation of treatment were excluded. This supports previous findings of reduced morbidity in the early years of life of children with cystic fibrosis who were detected by screening.[5][6] It may introduce an element of cost effectiveness into screening for cystic fibrosis, but to assess this accurately it would be necessary to know the cost of treatment for patients whose lives were extended by early identification and treatment, if this proved to be the case.

All four deaths occurred in unscreened patients. While this illustrates that infants with cystic fibrosis are vulnerable at a young age, it does not allow any deductions to be made about the effect of screening, as three of the infants died at about the mean time of the recognition of cystic fibrosis by our screening programme—that is, at 2–3 months.

Whatever the effect of earlier diagnosis on the clinical state of children with cystic fibrosis there is little doubt that genetic counselling should be made available to affected families as soon as possible,[24] to enable them to make considered decisions on their future family plans.[25]

Although the screening programme ended in December 1989 we plan to follow up the identified cohorts of patients for many years. This should provide the answer to the question of whether early diagnosis and treatment are beneficial to children with cystic fibrosis.

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Controversies in the management of gastroschisis: a study of 40 patients

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Abstract

Forty infants with gastroschisis were referred to two paediatric surgeons during a 13 year period. Overall survival was 90%. Nine patients were transferred in utero and 31 were referred postnatally. Birth weights, gestational ages, and Apgar scores were similar for both groups. Primary closure of the defect was successfully achieved in seven (78%) patients in the prenatally transferred group compared with 17 (55%) in the postnatal group. Significantly less postoperative assisted ventilation, and a trend in favour of early discharge home, were noted after prenatal transfer. Problems arising during postnatal transfer may have contributed to these differences. No major differences resulting from the mode of delivery were identified. Patients treated by primary closure fared significantly better than those undergoing staged repairs with prosthetic material. Prospective randomised studies are required to confirm these findings.

The incidence of gastroschisis is approximately 1/10 000 births. In both Europe and the United States there has been an apparent increase in incidence during the past decade.[1] Major controversies affecting the obstetrician, neonatologist, and paediatric surgeon surround the management of gastroschisis. Uncertainty clouds the relative merits of prenatal compared with postnatal transfer, caesarean section compared with vaginal delivery, and primary compared with serial closure techniques. This retrospective study of 40 recently treated neonates attempts to define significant differences in outcome between these groups of patients.

Table 1 Comparison of prenatal and postnatal transfer groups

	Prenatal transfer: group 1 (n=9)	*Postnatal transfer: group 2 (n=31)*
Mean (SD) gestational age (weeks)	37·8 (1·5)	36·8 (2·6)
Mode of delivery (caesarean:vaginal)	1:8	10:21
Mean (SD) birth weight (g)	2317 (517)	2329 (563)
Median Apgar scores (5 min)	9	8
Mean (SD) age at operation (hours)	4·6 (3·0)	6·7 (3·1)*
No (%) with successful primary closure	7 (78)	17 (55)
No (SD) days of postoperative ventilation	0·9 (1·5)	5·8 (6·7)†
No (SD) days to full enteral feeding‡	29·9 (13·5)	32·6 (15·9)
No (SD) days hospital stay‡	35·9 (13·2)	50·5 (27·3)
Survival	9 (100%)	27 (87%)

*0·1>p>0·05 (no significant difference: unpaired *t* test).
†p<0·02 (unpaired *t* test); primary closures only.
‡n=33; excludes four postoperative deaths and three survivors with associated intestinal atresia in group 2 (no significant difference: unpaired *t* test).

Patients and methods

A retrospective analysis was undertaken of the case notes of a consecutive series of 40 neonates with gastroschisis treated during the past 13 years. In some cases this was supplemented by the obstetrician's notes and interviews with mothers. Those transferred prenatally were delivered and underwent surgery at a single institution whereas those transferred postnatally underwent surgery at either of the two Hospitals for Sick Children or at University College Hospital, London. Primary abdominal wall closure was performed whenever possible but a staged repair with a prosthetic patch or silo was employed when necessary.

The median maternal age was 21 years (range 17–31) and 29 mothers were primiparous, which accords with known epidemiological data.[1] Nine infants underwent surgery after prenatal transfer (group 1) and 31 after postnatal referral (group 2).

Statistical analyses were by the χ^2 test, the unpaired *t* test for normally distributed data, or the Mann-Whitney U test for non-parametric data.

Results

Mean gestational ages, birth weights, and Apgar scores at 5 minutes were similar in both groups (table 1). Successful primary closure was achieved in 7/9 (78%) patients in group 1 compared with 17/31 (55%) in group 2 (no significant difference using the χ^2 test with Yates's correction). Patients in group 1 tended to undergo surgery sooner after birth, were ventilated for significantly less time, and tended to be discharged home earlier than those in group 2 (table 1).

Although only nine (23%) patients were referred prenatally, gastroschisis had been detected prenatally in 21 (53%). Successful primary closure was achieved in 12 (57%) infants diagnosed prenatally and in nine (47%) of those who had not been detected prenatally. There was no significant difference in the frequency of primary closure after delivery by caesarean section (8/11) compared with that after vaginal delivery (16/29) and there were no significant differences in the three measures of postoperative morbidity. Four of the 11 caesarean sections were performed electively because of the prenatal diagnosis of gastroschisis, two were for breech presentation, and the remainder were for fetal distress. There was no association between the extent of evisceration (small bowel and colon with or without stomach

Table 2 Comparison of primary and serial closure groups

	Primary closure (n=21)	*Serial closure (n=12)*	*Significance*
Mean (SD) gestational age (weeks)	36·6 (2·8)	37·7 (1·6)	NS
Mode of delivery (caesarean:vaginal)	7:14	3:9	NS
Mean birth weight (g)	2296 (625)	2350 (410)	NS
Median Apgar scores (5 min)	9	9	NS
Mean (SD) age at operation (hours)	6·2 (3·8)	6·1 (2·2)	NS
No (SD) days of postoperative ventilation	3·9 (6·1)	7·2 (12·3)	NS
No (SD) days to full enteral feeding	26·7 (12·9)	40·9 (15·0)	p<0·02
No (SD) days total parenteral nutrition	21·1 (13·2)	32·4 (14·4)	p<0·05
No (SD) days hospital stay	37·3 (17·6)	62·8 (28·2)	p<0·02

n=33; excludes four postoperative deaths and three survivors with associated intestinal atresia.

and pelvic viscera) and the ability of the surgeon to effect successful primary closure.

Excluding the four postoperative deaths and the three survivors with associated intestinal atresia, patients undergoing primary closure were ventilated for no longer than those receiving staged repair but achieved full enteral feeding significantly earlier and were discharged home sooner (table 2).

Associated congenital anomalies were uncommon (table 3) being detected in only 13 (33%). No chromosomal abnormalities were identified in the four tested patients with multiple anomalies.

Several neonates undergoing postnatal transfer arrived in poor condition (table 4). Bilious vomiting, due to an absent or inadequately sited/sized nasogastric tube, occurred in six, but fortunately none of these had evidence of pulmonary aspiration. The cooling of 'warm' saline packs used to cover the eviscerated intestine resulted in appreciable hypothermia in five and uncorrected fluid and plasma losses from the exposed intestine demanded urgent colloid resuscitation in four neonates.

*Table 3 Associated congenital anomalies in 13 patients with gastroschisis**

Gastrointestinal:	
Jejunoileal atresias (two high jejunal atresias, one ileal, and one apple peel variant)	4
Meckel's diverticulum	2
Other anomalies:	
Undescended testes (two unilateral and two bilateral)	4
Inguinal hernias (one unilateral and one bilateral)	2
Cardiac (ventriculoseptal defects)	3
Arthrogryposis multiplex with congenital hip dislocation	1

*Errors of intestinal rotation have been excluded.
Some infants had more than one associated anomaly.

Table 4 Complications of management in 40 infants with gastroschisis

Complications of management	*No of infants†*
Complications during postnatal transfer:	
Inadequate nasogastric drainage	6
Hypothermia (core temperature ≤35·0°C)	5
Appreciable hypovolaemia	4
Major postoperative complications:	
Bowel ischaemia/necrosis after primary closure	2
Partial dehiscence or sepsis of patch/silo	5
Cannula/long line sepsis	5
Necrotising enterocolitis	4
Convulsions	4
Long term complications*	
Failure to thrive (<3rd centile at 1 year)	7
Incisional hernias	4
Symptomatic gastro-oesophageal reflux	4
Neurological impairment	3

*Eight infants under the age of 1 year and four early deaths are excluded.
†Some infants had more than one complication.

The overall initial survival rate after gastroschisis repair was 90%. Of the four deaths, two were due in part to bowel ischaemia after 'tight' primary closure. Subsequent attempts to redeem the situation with a silo were unsuccessful. One death was from status epilepticus in an infant who had required massive intestinal resection and stomas for gastroschisis complicated by midgut volvulus necessitating prolonged intravenous nutrition complicated by hypocalcaemia, septicaemia, and disseminated intravascular coagulation. The remaining patient died aged 6 weeks from extensive neonatal necrotising enterocolitis after staged silo repair. There was one late death from acute bronchiolitis in a 6 week old infant who had been discharged home three weeks after an uneventful primary repair.

Discussion

There are three outstanding controversies in the management of neonates with gastroschisis: firstly, whether prenatal transfer confers any advantage to the prenatally diagnosed patient; secondly, whether the patient should be delivered vaginally or by caesarean section; and thirdly, whether the anterior abdominal wall defect is optimally managed by primary or serial closure. It is difficult to resolve these questions by a retrospective study but until prospective randomised trials have been undertaken, retrospective analyses provide the only source of data for clinical guidelines.

Despite statistical limitations, there was a clear trend in the prenatal transfer group in favour of more frequent successful primary closure, less postoperative ventilation, and reduced hospital stay. There are many possible reasons for this, including earlier surgery, but a likely major factor is the preoperative condition of the infant, as this is an important determinant of postoperative outcome.[2] Hypothermia, hypovolaemia, and inadequate nasogastric drainage were readily identifiable complications of postnatal transfer leading to delays in surgery. Several layers of 'cling-film' wrapped around the infant successfully preserved central temperature and reduced evaporative losses whereas the use of saline soaked swabs resulted in rapid cooling. Transparent plastic sheeting also allows ready inspection of the bowel and the early recognition of intestinal ischaemia, which was noted on arrival in two of our patients. It is uncertain as to whether or not the postnatal transfer of infants under optimal conditions would eliminate the apparent advantages of prenatal transfer. A protocol designed to minimise the hazards of postnatal transfer of the infant with gastroschisis is suggested in table 5. The maternal morbidity resulting from 'in utero transfer' should be recognised, but could not be analysed in this study.[3 4]

The obstetric management of gastroschisis has been discussed by several authors.[5–7] In the present study, there were no discernable differences in outcome between infants delivered by caesarean section and those delivered vaginally and it is accepted that there is greater maternal morbidity associated with delivery by caesarean section.[8] Until prospective randomised trials

Table 5 A protocol for postnatal transfer in gastroschisis

- Early liaison with neonatal surgical unit
- Adequately sited size 8–10 French gauge nasogastric tube on free drainage with aspiration every 15 minutes
- Double 'cling-film' wrap of the abdomen including exposed intestine
- Colloid infusion (10–20 ml/kg)
- Broad spectrum prophylactic antibiotics
- Meticulous temperature control in transport incubator
- Consent for surgery/vitamin K intramuscularly/maternal blood sample
- Rapid transport of the infant after initial resuscitation

have been conducted, we would concur with others that vaginal delivery does not appear to adversely affect outcome,[7 9–11] and that the mode and timing of delivery should be determined by indications other than the presence of a fetal abdominal wall defect.

The surgical management of the abdominal wall defect has generated much discussion among paediatric surgeons. Attitudes range from those who advocate primary closure whenever possible because of the higher mortality and morbidity rates of staged repair (principally sepsis, sac separation, and the need for multiple operative procedures)[12–16] to those who recommend serial closure with prosthetic material because of the hazards of tight primary closure (principally intestinal ischaemia, respiratory and renal impairment).[17–20] In this study primary closure was attempted whenever it was considered to be safely possible. Adopting this policy based on subjective clinical judgment, infants undergoing primary closure were more quickly established on full enteral feeding and discharged home significantly earlier than those treated by staged repair.[21 22]

Two of the four deaths were partly related to excessively tight primary closure resulting in intestinal ischaemia but nevertheless, intestinal infarction may occur as a complication of staged repair.[18] Large defects with gross visceroabdominal disproportion clearly require staged repair.[23] Intraoperative assessment of intraabdominal pressure, pulmonary compliance, or haemodynamic parameters may provide valuable objective information that would optimise closure technique in borderline cases.[24 25]

This study confirms the generally good prognosis of infants with gastroschisis,[2 10 14 22] which is in sharp contrast to that of infants with exomphalos.[1 10 26] Major cardiac anomalies and abnormal karyotypes are unusual in infants with gastroschisis and associated abnormalities are principally gastrointestinal and amenable to corrective surgery.[10 26] Nevertheless, terminations of affected pregnancies are not uncommon.[10 26] Now that it is possible to distinguish between gastroschisis and exomphalos using prenatal ultrasonography in major antenatal diagnostic centres,[9] guidelines for the termination of pregnancy need to be reconsidered. The retrospective data in this study suggest that when feasible primary closure may be advantageous, that there appears to be no benefit from delivery by caesarean section and that prenatal transfer may be associated with improved results. When prenatal transfer is impractical, optimum postnatal transfer is mandatory (table 5). Prospective randomised trials are the only method of satisfactorily addressing these issues.

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Nutrition and bronchopulmonary dysplasia

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Abstract

Twenty two babies who developed bronchopulmonary dysplasia were compared with 22 babies matched for gestational age who did not. Those with bronchopulmonary dysplasia weighed less at birth and had lower energy intakes from day 7 to day 56. Undernutrition before and after birth is a major problem in babies who develop bronchopulmonary dysplasia.

Advances in neonatal intensive care such as surfactant replacement have led to increased survival rates among very small preterm babies with respiratory distress syndrome, but many of these babies develop bronchopulmonary dysplasia.[1] One of the reasons for this may be that prolonged mechanical ventilation is required because these babies are very small and may be undernourished. We therefore decided to compare energy intakes over the first two months of life in a group of babies who developed bronchopulmonary dysplasia with a group of babies matched for gestational age who did not.

Patients and methods

From January 1987 to December 1988, 129 very low birthweight (VLBW) infants were born in, or transferred on the first postnatal day to, this hospital. Thirty two babies were either transferred back to their referral unit before the age of 30 days or died. Clinical details, serial measurements of energy intake, and outcome data were obtained for the remaining 97 infants. Energy intakes were recorded from medical and nursing records, and are actual amounts taken rather than those prescribed. Statistical analysis was by the Mann-Whitney U test and the χ^2 test as appropriate.

Bronchopulmonary dysplasia was diagnosed if the babies were dependent on oxygen for 28 days or longer and on radiological findings.[2] Twenty two infants who developed bronchopulmonary dysplasia were compared with 22 infants matched for gestational age who required mechanical ventilation for more than three days for respiratory distress syndrome but who did not develop bronchopulmonary dysplasia.

Results

Table 1 shows the characteristics of the two groups of infants. Those who developed bronchopulmonary dysplasia weighed significantly less at birth, indicating pre-existing intrauterine undernutrition. There were no significant differences in the incidences of patent ductus arteriosus or pulmonary air leaks (pulmonary interstitial emphysema or pneumothorax).

From 10 days onwards the energy intake of the babies with bronchopulmonary dysplasia was significantly lower than that of the control babies (table 2). Infants who developed bronchopulmonary dysplasia started enteral feeds significantly later than the control babies (median (range) times of 19 (6–71) and 9 (3–39) days, respectively). They required a median of 88 (37–130) days to reach and maintain full enteral feeds, compared with 47 (20–120) days for the control babies. Intravenous feeding was required for a median of 75 (29–126) days compared with 39 (14–111) days, and lipid emulsion was given for a median of 44 (0–123) days compared with 22 (3–95), respectively. These values are all significant ($p<0·05$).

Table 2 Mean (SD) energy intake (kJ/kg/day)

Day	*Babies with bronchopulmonary dysplasia (n=22)*	*Babies without bronchopulmonary dysplasia (n=22)*
7	278·8 (72·7)	322·3 (94·9)
10	270·9 (65·2)**	357·4 (66·9)
14	321·9 (61·0)*	367·8 (60·6)
28	357·0 (53·9)	387·5 (81·1)
56	364·5 (66·0)**	455·6 (63·5)

*$p<0·05$, **$p<0·001$.

Table 1 Clinical characteristics and outcome of babies requiring mechanical ventilation for respiratory distress syndrome

	Babies with bronchopulmonary dysplasia (n=22)	*Babies without bronchopulmonary dysplasia (n=22)*
Mean (SD) gestational age (weeks)	26·9 (1·7)	27·4 (1·7)
Mean (SD) birth weight (g)	839 (229)*	1015 (170)
No (%) of babies small for gestational age	8 (36)	5 (23)
No (%) of boys	12 (55)	9 (41)
Median (range) duration of supplementary oxygen (days)	109 (33–268)**	37 (9–97)
Median (range) duration of assisted ventilation (days)	68 (19–206)**	19 (4–86)
No (%) who developed patent ductus arteriosus	10 (45)	15 (68)
No (%) who died	5 (23)	0

*$p<0·05$, **$p<0·001$.

Discussion

Undernutrition is a serious problem in VLBW infants who develop bronchopulmonary dysplasia.[3] We have found that this may begin before birth and have a significant effect on the energy reserves of the very preterm infant. The appropriately grown infant weighing 1000 g at birth has a body composition containing less than 2% fat, compared with 16% at full term.[3] Intrauterine undernutrition, which occurred in the babies who developed bronchopulmonary dysplasia, lowers these energy reserves still further.

Poor energy reserves will be exacerbated by poor energy intake after birth. The American Academy of Pediatrics has recommended that a heathly preterm infant should receive an energy intake of 501·6 kJ (120 kcal)/kg/day.[4] Why have we had such difficulty in reaching this figure? After analysis of our data we think that there are several reasons for this. There is often a need to restrict fluids in critically ill babies, in those with patent ductus arteriosus, and in babies with established bronchopulmonary dysplasia. These infants also commonly will not tolerate standard dextrose infusions. Furthermore, lipid infusions are often delayed and there may be frequent periods of lipid free feeding because of concerns about respiratory function, hyperbilirubinaemia, and sepsis. Our policy is to delay the start of enteral feeding until the infant's vital signs are stable, ventilator settings are being reduced, and umbilical arterial catheters have been removed. Delay in achieving full enteral feeds often occurs in VLBW infants because they have abdominal distension or features suggestive of necrotising enterocolitis. Finally, there may be technical problems such as the length of 'down time' between replacement of intravenous cannulas.

It is also probable that there are increased metabolic demands in sick preterm infants that require mechanical ventilation, although these have not been measured. Studies in oxygen dependent infants with bronchopulmonary dysplasia, however, have shown that they have an increase in energy expenditure of 25%.[5]

Recently, Frank hypothesised that the early provision of adequate nutrition may be a key prophylactic measure for limiting the risk of development of bronchopulmonary dysplasia.[3] Factors thought to be important in the pathogenesis of bronchopulmonary dysplasia—hyperoxia, barotrauma, infection, and pulmonary immaturity—are all adversely affected by undernutrition. If inspiratory muscles are deprived of substrate the resultant fatigue will lead to failure of the respiratory muscle pump. Undernutrition has been shown to alter ventilatory muscle function in animals and man.[6] Improving nutritional state allows more rapid weaning of seriously ill adult patients from mechanical ventilation but similar studies have not been carried out in babies.

Our study shows that in both the acute phase when bronchopulmonary dysplasia is developing and in the chronic phase when infants with bronchopulmonary dysplasia remain dependent on the ventilator there is evidence of undernutrition. Intrauterine growth retardation, poor energy reserves, and increased metabolic demands are also important. A prospective randomised trial is needed to find out if improvement in nutritional state will reduce the incidence and severity of bronchopulmonary dysplasia.

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Endotracheal resuscitation of neonates using a rebreathing bag

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Abstract

Thirty asphyxiated neonates were resuscitated endotracheally with an anaesthetic rebreathing bag. The system was not limited either by pressure or by volume and chest movement was used as the criterion for adequate inflation. Inflation pressure and flow were recorded during resuscitation, and flow was integrated to obtain volume. Median mean pressure over the first 10 inflations was 40 cm H_2O and this dropped during later resuscitation to 29 cm H_2O. The volume delivered did not change significantly, so volume divided by pressure increased from a median of 0·18 to 0·35 ml/kg/cm H_2O. Fourteen infants formed part of their functional residual capacity with artificial ventilation and five with spontaneous breaths. Eleven infants showed no evidence of functional residual capacity formation. In the 22 preterm infants there was a strong association between absence of functional residual capacity formation and later hyaline membrane disease that required ventilation.

We suggest that pressures of more than than 30 cm H_2O may be helpful during initial resuscitation and that there should be further study of devices using positive end expiratory pressure for resuscitation of preterm infants.

Despite recent advances in management, birth asphyxia remains a major cause of mortality and morbidity.[1] Though there is much interest in it, comparatively little attention has been paid to the methods of resuscitation and their mechanisms. Pioneering studies by Ditchburn *et al*,[2] Hey and Kelly,[3] and Hull[4] used a volume limited system and were unable to measure the volumes of individual inflations. Hull stated that 30 cm H_2O was a suitable pressure at which to set the 'blow off' valve during resuscitation, but recognised that this would not be adequate for some infants.[4]

Boon *et al* studied resuscitation using a T piece and finger occlusion technique.[5] Though they limited pressure to 30 cm H_2O, their work did yield important information about the response to resuscitation[5] and formation of the functional residual capacity.[6]

All such previous work, however, has limited either volume or pressure, which may have significantly affected the results. In addition, improvements in obstetric care and maternal anaesthesia, and greater use of neonatal mask resuscitation, have led to a reduction of intubation rates for resuscitation.[7] The characteristics of babies requiring intubation have, therefore, changed during recent years and so also have their requirements for effective resuscitation. Finally, endotracheal resuscitation using a bag system is still commonly used and may give different results from a finger occulsion technique. Indeed, a slow rise inflation has been shown to be more effective than a square wave.[8]

We have therefore studied endotracheal resuscitation of asphyxiated neonates using a bag for inflation and a system that limits neither pressure nor volume.

Subjects and methods

Babies who required endotracheal resuscitation were intubated with a shouldered Portex endotracheal tube. The largest tube possible (size 2·5 or 3·0) was used for each individual baby to avoid problems of leak around the endotracheal tube. The lungs of intubated babies were inflated using a 0·75 l anaesthetic rebreathing bag (Medishield) connected with a Fleisch 0 pneumotachograph to the proximal end of the endotracheal tube (fig 1). Tidal flow was measured from the pneumotachograph with a Furness Controls differential pressure transducer (FCO40, range±20 mm Hg). Inflation pressure was measured from a Furness Controls transducer (FCO40, range±1000 mm Hg) attached to the connecting piece between the endotracheal tube and the pneumotachograph. The 63% response time of the pneumotachograph (calculated by bursting balloons connected to the system) was 8 ms, giving a 3 dB/octave loss at 20 Hz. The response time of the pressure transducer was similar (10 ms) giving a 3 dB/octave loss at 16 Hz.

Pressure and flow signals were recorded on to tape during resuscitation, and flow subsequently digitally integrated to obtain volume.

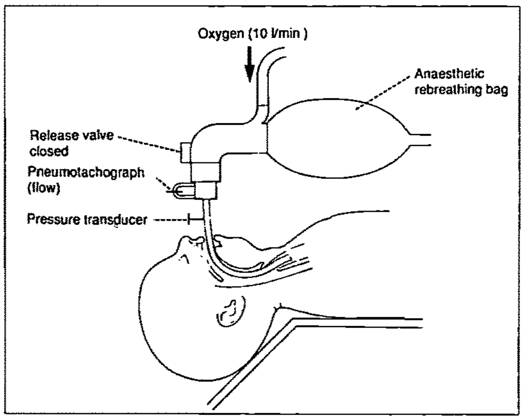

Figure 1 Diagram of resuscitation system.

The response of the equipment was linear to within 5% over a range of pressures of 5 to 50 cm H_2O and volumes of 2 to 50 ml. After each resuscitation the calibration was checked with a water manometer to measure 20 cm H_2O pressure and with a syringe to measure 10 ml volume.

During resuscitation the blow off valve on the rebreathing bag was kept closed. The end of the bag was open, however, and was controlled by the fingers of the resuscitator (CJU in all cases). The bag was supplied with a flow of oxygen of 10 l/min from a cylinder with no blow off valve in line. Chest movement was observed closely and the bag gently squeezed until inflation was observed (fig 1). A rate of inflation of 40 breaths/minute was our aim, and the inflation time was prolonged as much as possible with a bag volume of 0·75 l.

The whole system was portable but some warning was necessary; only high risk deliveries were attended, therefore. If the delivery was elective, then the procedure was discussed with the parent(s) beforehand.

Eighty two high risk deliveries were attended between February 1988 and June 1989. Thirty two infants required intubation for resuscitation, but only 30 were successfully studied as two twins were born in such rapid succession that they had to be resuscitated conventionally. Babies were only given endotracheal resuscitation if they were apnoeic with an Apgar score of 4 or less after one minute, or had failed to respond to intermittent positive pressure ventilation (IPPV) by mask.[9] Preterm infants were not intubated electively.

The modes of delivery are shown in table 1. Fifteen mothers were in labour and 15 were not. Sixteen boys and 14 girls were resuscitated, with a median birth weight of 1760 g (range 580–3980) and gestation of 33 weeks (range 26–42). Twenty two of the infants were preterm. Eighteen of the 30 made some respiratory effort, usually weak, before becoming apnoeic and eight infants were given IPPV by mask before intubation. Four infants required suction for meconium below the cords before the initiation of endotracheal IPPV. The median 1 minute Apgar score was 3 (range 1–8) and all resuscitations were successful, with a median 5 minute Apgar score of 8 (range 5–9). None of the infants required external cardiac massage and only one needed treatment with intravenous dextrose and sodium bicarbonate while on the resuscitaire.

After resuscitation, pressure and volume signals were played from the tape on to a chart recorder (Devices) with a paper speed of 10 mm/s. Values of pressure and volume were calculated manually from the beginning of the trace and compared with a period just before the onset of regular respiration, usually at around 1 minute. The mean value from 10 inflations was obtained from each part of the trace but only those where the pressure and volume peaks coincided were used for analysis, necessitating the use of smaller numbers on four occasions. Paired observations were compared with the Wilcoxon ranked sum test, and unpaired data with the Mann-Whitney U test. Variables were analysed for the effect of gestation and birth weight using regression analysis. Outcome was analysed with respect to presence or absence of functional residual capacity formation using Fisher's exact test. Numbers of effective initial inflations were compared with historical data with the χ^2 test. Approval for the study was given by the Nottingham ethics committee.

Results

Full results are shown in table 2. The median rate of inflation was 48 breaths/minute during the early part of resuscitation, with a median inspiratory time of 0·51 s. The maximum pressure of any single inflation ranged up to 73 cm H_2O. The median mean pressure during the early part of resuscitation was 40 cm H_2O, and this dropped to 29 cm H_2O during later resuscitation ($p<0·0001$). The inflation pressure may have dropped as the baby responded simply as a result of relief on the part of the resuscitator. Volumes delivered increased slightly as the pressure dropped, however, from a median of 8·6 to 9·7 ml/kg; this was not significant. Volume was divided by pressure to give a measure of the efficiency of resuscitation; this was not true compliance as the volume trace did not plateau. Median volume/pressure virtually doubled during resuscitation, from 0·18 to 0·35 ml/kg/cm H_2O ($p<0·0001$). Median inflation volume for the first inflation was 8·7 ml/kg (range 0–23·4), which was similar to the median mean over the first 10 inflations. This was significantly better than historical data from Boon *et al* who showed a median inflation volume for the first breath of 4·6 ml/kg (range 0–18·4) using a blow off pressure of 30 cm H_2O and an occlusion technique ($p<0·0001$).[6]

The number of the first three inflations that yielded an arbitrary volume of 4·4 ml/kg was also calculated by the method of Hoskyns *et al.*[10] This was chosen to be roughly two anatomical dead spaces. Overall, 58 of 90 inflations (64%) delivered at least 4·4 ml/kg. Among the preterm infants the proportions were similar, with 43 of 66 inflations (65%) reaching 4·4 ml/kg. This compares favourably with historical data from Hoskyns *et al*, who also used a pressure blow off valve set at 30 cm H_2O and an occlusion technique.[10] In their study of 21 preterm infants only 18 out of 63 initial inflations (29%) reached 4·4 ml/kg, a significantly smaller proportion than in the present study ($p<0·001$).

Table 1 Mode of delivery

	No of infants
Emergency caesarean section	19
Breech delivery	5
Elective caesarean section	3
Normal vaginal delivery	2
Forceps delivery	1
Total	30

Table 2 Pressures and volumes during early and late resuscitation

	Median	*Range*
Maximum pressure (cm H_2O)	50	33–73
Early mean pressure (cm H_2O)	40	28–60
Early volume (ml/kg)	8·6	1·1–22·5
Early volume/pressure (ml/kg/cm H_2O)	0·18	0·03–0·42
Late mean pressure (cm H_2O)	29	18–42
Late volume (ml/kg)	9·7	2·1–20·4
Late volume/pressure (ml/kg/cm H_2O)	0·35	0·06–0·81

The results of the pressure/volume relationships were analysed by simple regression analysis to see if gestational age, birth weight, or Apgar scores had an effect. No trends were apparent; pressures required seemed to be randomly distributed among the babies.

Preterm infants required neither higher nor lower pressures, and whether or not the mother was in labour made no significant difference to any of the variables listed in table 2.

Figure 2 shows the initial resuscitation of a preterm infant of 32 weeks' gestation. More volume goes in than out over the first four inflations giving a stepwise formation of the functional residual capacity. She did not breathe before intubation. If she had, then clearly the formation of the functional residual capacity could have been missed. In 14 infants the functional residual capacity was formed in this stepwise fashion with artificial ventilation, but in 11 there was no evidence of functional residual capacity formation. A different pattern is seen in fig 3, which shows the initial resuscitation of an infant of 30 weeks' gestation. He did not breathe before laryngoscopy but took two gasps immediately after intubation. Part of his functional residual capacity was formed with these spontaneous breaths, but little added with the subsequent artificial ventilation. Five infants formed their functional residual capacities in this way, with spontaneous but not artificial breaths. There were no significant differences in the pressure/volume relationships between those babies who were seen to form functional residual capacities and those babies who were not.

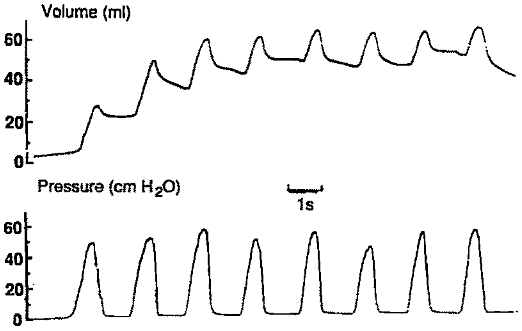

Figure 2 Resuscitation trace from case 25. Inspiration is upwards on the volume trace. Note formation of functional residual capacity over the first four inflations.

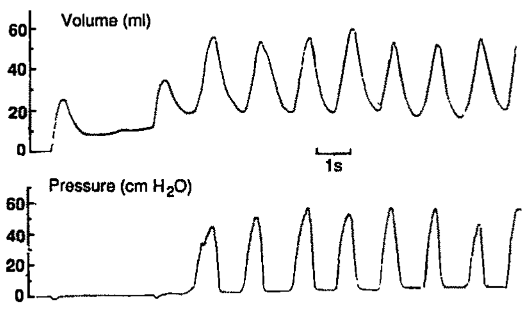

Figure 3 Resuscitation trace from case 22. Inspiration is upwards. Note two spontaneous gasps before onset of IPPV with part of functional residual capacity being formed with the spontaneous, but not artificial ventilation.

All but five infants were admitted to the neonatal intensive care unit, mainly because of prematurity or respiratory disease. Only one baby was admitted simply because of the birth asphyxia, and no infant developed more than mild postasphyxial encephalopathy. Despite the high initial pressures there were no pneumothoraces and all but five infants had a chest radiograph taken. Seven infants were ventilated for hyaline membrane disease of whom four died. One baby of 26 weeks' gestation was ventilated electively after resuscitation but found to have no respiratory disease and he was successfully extubated at 24 hours. There were three other deaths in infants who did not have hyaline membrane disease and none of these was related to the asphyxia. Two of these infants had congenital abnormalities (one had Edwards' syndrome and one had a diaphragmatic hernia) and the other died of overwhelming sepsis at the age of 10 days.

There was no correlation between the use of higher initial pressures or more effective volume/pressure relationships and later outcome, which was not surprising as we were using a system with no pressure limit and as the babies with stiffer lungs needed higher pressures to achieve visible chest movements.

There was, however, an apparent effect of functional residual capacity formation on outcome, particularly with respect to hyaline membrane disease, as none of the four babies who died with hyaline membrane disease had shown evidence of functional residual capacity formation. We therefore analysed the results of the 22 preterm infants separately (table 3). There was a significant association between hyaline membrane disease requiring ventilation and the absence of functional residual capacity formation, and conversely between its presence and mild (requiring headbox oxygen only) or no disease ($p=0{\cdot}02$).

Discussion

The results of this study have shown that a median pressure of 40 cm H_2O is required to inflate the chests of intubated, asphyxiated neonates during the first 10 inflations. This is not surprising as during spontaneous first breaths babies generate negative intrathoracic pressure of 40 to 100 cm H_2O.[11] The required pressure falls as resuscitation continues, and in our study the median pressure dropped to 29 cm H_2O just before regular respiration started. This confirms previous work with a system in which volume was limited.[4] The lungs at

Table 3 Relationship between absence of formation of functional residual capacity and later severe hyaline membrane disease in 22 preterm infants

	Formation of functional residual capacity	*No functional residual capacity seen*	*p Value**
Mild or no hyaline membrane disease	10	3	0·02
Severe hyaline membrane disease (requiring ventilation)	2	7	

*Fisher's exact test (two tailed).

birth are filled with fluid resulting in a low initial compliance, but as this clears the compliance increases and lower pressure may inflate the chest.[4 8]

We have also shown that considerable improvements in ventilation can be achieved over the first one to three breaths using a rebreathing bag with no pressure limit, compared with historical data using a finger occlusion technique and a pressure limit of 30 cm H_2O.[6 10] Clearly there are drawbacks to using historical data for comparison, but the methods for measuring pressures and volumes at resuscitation were similar in all the studies. The more effective initial ventilation we have observed may not necessarily be the result of the higher pressures used. Both the inflation time and waveform of the inflation pressure are known to be important factors.[8] The inflation time in our study was actually shorter, however, (median 0·51 s) than the 1 second used by both Boon *et al* and Hoskyns *et al*.[6 10] The waveform produced by the rebreathing bag may have been more effective than a square wave, though whether this is important with a shorter inflation time is debatable. The improvement in slow rise inflation shown by Vyas *et al* was over 3–5 s.[8] We therefore believe that it is the increased pressures that we used that resulted in the improved ventilation. Improved early ventilation may also be achieved by the use of a longer inflation time but clearly this may result in a lower frequency of inflation and lower minute ventilation, compared with the shorter inflation times used in the present study.[8]

The use of an anaesthetic rebreathing bag in this study permitted us to observe chest movement during a slow rise inflation and thereby avoid excessive pressure. We would have liked to have used a longer inflation time but this proved difficult with the volume of the bag. The arguments for and against the use of rebreathing bags have been discussed by Kanter.[12] He believed that they had advantages in experienced hands and especially when ventilating through an endotracheal tube. The technique is not easy to learn, however, and we would feel that it is inappropriate for rebreathing bags to be used routinely by inexperienced junior medical staff or midwives.

Self inflating resuscitators are also commonly used but these also have limitations. They have been shown in experienced hands to deliver inflation times of only up to half a second[7]; in inexperienced hands we have noted considerably shorter inflation times. They tend to have unreliable blow off valves and may not deliver the required concentration of oxygen.[13] They are also clumsy to use, especially when connected to an unfixed endotracheal tube. Clearly, improvements to the available self inflating resuscitation bags are necessary before their widespread use can be recommended.[14]

We continue to use the finger occulsion technique routinely for both endotracheal [5] and face mask resuscitation.[10] This allows the use of longer inflation times, can be done with one hand, is easy to learn, and is generally effective.

It is difficult to extrapolate from the group of high risk infants resuscitated in this study to the general population of intubated neonates. Careful consideration should be given, however, to increasing the blow off pressure during initial resuscitation to at least 40 cm H_2O. Indeed, half our infants required mean initial pressures greater than this before chest inflation occurred. If chest movement is poor and the baby is slow to respond to resuscitation, then an increase in inflation pressure may well be helpful. Nevertheless there is a worry that in inexperienced hands such a high pressure may be used later in resuscitation and be harmful. Indeed, evidence from 30 resuscitations is not sufficient to ensure the safety of using higher pressures, even during initial resuscitation; further work is necessary to draw up new guidelines for endotracheal resuscitation.

Previous studies have not been able to correlate outcome with any of the measurements made during resuscitation. We have shown a strong correlation between absence of functional residual capacity formation in preterm infants and later hyaline membrane disease requiring ventilation. This association was confounded by the fact that some babies breathed before intubation and therefore functional residual capacity formation may have been missed. This makes the strong association seen here even more impressive. The ability of such a system to predict severe hyaline membrane disease would, however, be limited by any cries that the baby made before intubation. It is interesting to postulate, though, that the lack of functional residual capacity formation is the result of surfactant deficiency and that this can be detected within the first few breaths. It could also be assumed that atelectasis occurs between each inflation and makes resuscitation less efficient. It is therefore possible that a resuscitation device that delivered positive end expiratory pressure would be of benefit to preterm infants. Such a device would certainly warrant serious investigation.

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Atrial natriuretic factor and postnatal diuresis in respiratory distress syndrome

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Abstract

To find out if atrial natriuretic factor plays a part in the control of urine output during the initiation alone or throughout postnatal diuresis in neonates with respiratory distress syndrome, atrial natriuretic factor concentrations and clinical and renal variables were measured prospectively three times during the first three days of life in 13 premature infants. Atrial natriuretic factor concentrations rose significantly between the first and second sample times as did the urine output and output:input ratio. By the time that the third sample was taken, atrial natriuretic factor concentration had decreased significantly since the second sample had been taken, while urine flow was maintained. All subjects initiated a spontaneous diuresis that was related to the second concentration of atrial natriuretic factor. With partial correlation analysis a significant relationship was shown between the concentration of atrial natriuretic factor and the maintenance of urine output throughout the study period. Individual hormone concentrations did not, however, correlate with simultaneous renal variables. Changes in the concentrations of atrial natriuretic factor coincided with initiation of spontaneous diuresis in babies with respiratory distress syndrome, and may have a role in the complex mechanisms that maintain this diuresis.

Newborn infants with respiratory distress syndrome have a spontaneous diuresis during the first few days of life that results in a negative balance for sodium and water.[1] This diuresis may be an essential precursor of the improvement in lung function that occurs during the recovery phase of respiratory distress syndrome,[2] and failure to develop an early spontaneous diuresis has been implicated in the pathogenesis of bronchopulmonary dysplasia.[3] Though these observations have been confirmed in several reports, the mechanisms controlling the transient but pronounced increase in urine volume that occurs during the diuresis have not been identified.

Recently, atrial natriuretic factor has been described as a potent hormone exerting its principal effects on renal function.[4] A number of these effects resemble the changes in renal function and fluid balance described in neonates during the first few days of life. Specifically, atrial natriuretic factor is released from granules in the atrial myocytes in response to a rise in atrial volume.[5] This may occur in newborn infants because of a rise in atrial pressure caused by the changes in intracardiac and extracardiac blood flow after birth, or because there is a rise in atrial volume caused by a shift of intracellular fluid volume to the extracellular space during the postnatal period.[6] In addition, atrial natriuretic factor induces vasodilation and increases renal blood flow in previously constricted vascular beds[7]; similar haemodynamic changes in the renal vasculature occur during the transition from fetal to extrauterine life.[8] Infusions of atrial natriuretic factor cause pronounced natriuresis, kaliuresis, and diuresis in animals and man[9–11]; recent studies confirm that sodium, potassium, and water balances are negative during the spontaneous postnatal diuresis in infants.[1 12] Finally, high concentrations of plasma atrial natriuretic factor are found in newborn infants during the first week of life.[13 14]

These observations have led some investigators to speculate that atrial natriuretic factor may have an important role in the initiation,[15] or the subsequent maintenance, or both, of neonatal diuresis.[16]

This study was designed to investigate two hypotheses: firstly, that atrial natriuretic factor is associated with the initiation of the postnatal spontaneous diuresis in newborn infants; and secondly, that atrial natriuretic factor secretion maintains the diuresis until it is completed rather than acting during the initiation phase alone.

Patients and methods

To examine the hypotheses stated above, newborn infants admitted to the intensive care nurseries of the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania were considered eligible for study if they were born weighing 1500 g or more (necessary to obtain the required volumes for blood samples); if they were entered into study at 12 hours of age or less; if the 5 minute Apgar score was 6 or more; if an umbilical catheter had been placed with the tip below the heart under radiographic control; if they had not been treated with diuretics or cardiotonic drugs (for example epinephrine or dopamine)[17]; and if they had no congenital genitourinary or cardiac anomalies. All infants had clinical and radiological evidence of respiratory distress syndrome. All patients were nursed under radiant warmers. Medical management was conducted by house officers under the direction of the attending neonatologist. Informed consent was obtained from the parents before enrolment,

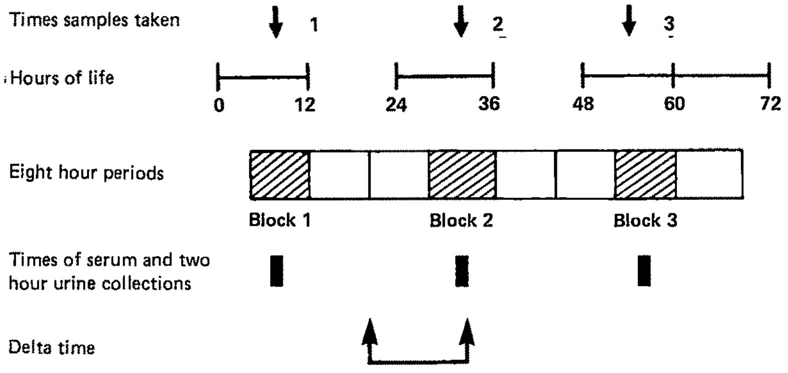

Figure 1 Diagrammatic representation of protocol. Block assignment (1, 2, or 3) of the eight hour periods depended on when the respective sample of atrial natriuretic factor was obtained. Urine and serum for chemical analyses were collected during the middle two hours of each block. Delta time was the time from the onset of diuresis (output:input >0·8 for a block) to the subsequent time when the next, sample of atrial natriuretic factor was taken.

and the study was approved by the Institutional Review Boards of both hospitals.

Plasma atrial natriuretic factor concentrations were determined from blood samples on three occasions: at less than 12 hours, between 24 and 36 hours, and at more than 48 hours of life. A sample of 2 ml of blood was drawn from the umbilical catheter, put into a test tube with potassium EDTA, and immediately centrifuged at 2500 g. After the addition of small amounts of antiproteases, the plasma was stored at −40°C. The samples of atrial natriuretic factor were extracted using ^{18}C Sep-pak cartridges with an 89% recovery. The extracted hormone concentrations were assayed by a specific radioimmunoassay against α human atrial natriuretic factor.[5] The normal pool plasma atrial natriuretic factor concentration with this assay was 7·62 pmol/l.

Parenteral and enteral fluid intake and urine volumes were recorded hourly and cumulative totals grouped into prospective sequential eight hour periods (fig 1). Urine output was determined by weighing premeasured nappies soon after voiding. Three separate blocks were defined as the eight hour periods during which each of the three samples of atrial natriuretic factor was obtained. During the middle two hours of each block urine was collected for chemical analysis after an initial observed void into a plastic bag adherent to the perineum. The collected pooled urine and simultaneously obtained serum samples were then analysed for electrolyte and creatinine concentrations and for osmolality. Electrolyte and creatinine concentrations were measured by an Ektachem analyser (Eastman Kodak). Freezing point depression (Wescor or OsMet Precision) was used to measure osmolality.

For each block, the measured serum and urine values were used to calculate renal functions (creatinine clearance, fractional sodium excretion, and free water clearance) according to standard formulas.[1] Fluid input and urine output (ml/kg/hour), the output:input ratio, and sodium and potassium excretion (mmol/kg/hour) were also calculated.

Ventilator settings and arterial blood gases from the midpoint of each block were recorded and used to calculate the alveolar-arterial oxygen gradient (A–aDO$_2$) (alveolar partial pressure of oxygen (P_AO_2) – arterial partial pressure of oxygen (P_aO_2); where P_AO_2= (fractional inspired oxygen (F_IO_2)×713) – arterial carbon dioxide tension (P_aCO_2)×(F_IO_2+ (1–F_IO_2)/0·8)).

Data were analysed using the Statgraphics software (Statistical Graphics Corporation). Concentrations of atrial natriuretic factor were analysed by the Friedman test and a non-parametric Tukey test. For parametric analysis hormone concentrations were transformed logarithmically to approximate a normal distribution. Mean values for each variable over the three eight hour blocks were analysed by ANOVA for repeated measures with the subject as a covariate. The α error for differences in means between two sampling times was determined by the Newman-Keuls test when the ANOVA showed significant differences among all three means. A probability of $<$0·05 was accepted as significant.

In testing the first hypothesis—the relationship between atrial natriuretic factor and the initiation of diuresis—the onset of diuresis was defined as the time at the beginning the block when the output:input ratio first exceeded 0·8.[2] This level is 1·4 standard deviations (92nd centile) above the mean of the output:input ratio preceding the diuretic period as determined by Bidiwala *et al* using an even stricter definition of diuresis.[12] The time of onset was then related to the log of the plasma atrial natriuretic factor concentration and the other measured variables from each of the three blocks by linear regression. The differences between the second atrial natriuretic factor sample time and the onset of the diuresis for each infant was defined as delta time.

To test the second hypothesis—that atrial natriuretic factor secretion is important to maintain the diuresis—a correlation matrix including all atrial natriuretic factor concentrations and the coincident measurements of blood chemistry, calculations of renal function, and respiratory variables was constructed using linear regression. A partial correlation matrix was then constructed to delineate further the maintenance of urine volume production during diuresis as a function of selected study variables held independent from the other study variables. Urine output was correlated independently with age at time of study (hours after birth), birth weight, fluid intake, log of the plasma atrial natriuretic factor concentration, renal function (creatinine clearance, free water clearance, and fractional sodium excretion), serum sodium concentration, and severity of respiratory illness (A–aDO$_2$). Log of the plasma atrial natriuretic factor concentration was independently tested against the same variables. Partial correlations determine the Pearson moment correlation coefficient between two variables while holding other variables constant.[18]

Results

Eighteen infants were enrolled in the study between April 1986 and November 1987. Three

Table 1 Mean (SEM) concentrations of atrial natriuretic factor and fluid balance from the three study blocks

	Block 1 *(n=13)*	*Block 2* *(n=13)*	*Block 3* *(n=11)*
Atrial natriuretic factor sample time (hour of life)	10·8 (0·4)	30·0 (0·6)	54·8 (0·8)
Atrial natriuretic factor (pmol/l)	54·3 (9·8)	92·0 (13·2)*	60·7 (13·8)†
Log of plasma atrial natriuretic factor (log pmol/l)	1·652 (0·078)	1·903 (0·069)*	1·690 (0·096)†
Fluid input (ml/kg/hour)	3·09 (0·15)	3·29 (0·15)	3·92 (0·28)‡§
Urine output (ml/kg/hour)	1·31 (0·32)	3·11 (0·50)*	3·65 (0·60)‖
Output:input ratio	0·44 (0·11)	0·94 (0·14)*	0·91 (0·12)‖

*p<0·001, block 2 *v* block 1; †=p<0·001, block 3 *v* block 2; ‡=p<0·02, block 3 *v* block 1; §=p<0·01, block 3 *v* block 2; and ‖=p<0·001, block 3 *v* block 1.

were excluded because their umbilical catheters were removed after the first blood samples were obtained. Two patients were withdrawn because they developed tension pneumothoraces during the study which may have acutely reduced blood return to the heart and affected atrial natriuretic factor concentrations. Two of the remaining 13 patients had only two samples of atrial natriuretic factor taken, but are included with appropriate corrections made in the analysis for missing data. Minor errors in the timing of urine and serum sampling also necessitated correction for missing data in the analysis.

The mean (SEM) weight of the 13 study subjects was 2030 (140) g and their gestational age was 33 (0·5) weeks. The mean (SEM) 5 minute Apgar score was 8 (1). All infants were receiving supplementary oxygen at entry into the study and 12 received positive pressure ventilation for between 17 hours and 27 days. During the study no subject had clinical evidence of a patent ductus arteriosus, a factor known to affect atrial natriuretic factor concentrations.[19]

Table 1 shows the time at which each of the three samples of atrial natriuretic factor was taken. The atrial natriuretic factor (and the log of the plasma atrial natriuretic factor) concentrations rose sharply between block 1 and block 2 (p<0·001), reflecting a rise in atrial natriuretic factor observed in 12 of the 13 subjects. The hormone concentrations fell between block 2 and block 3 (p<·001). As seen in table 1, the fluid intake rose over the three blocks, especially between blocks 2 and 3. Urine output and output:input ratio also rose but there were no significant differences in the latter two variables between block 2 and block 3. A continued diuresis (input:output ratio >0·8) was seen during block 3 in 7/11 subjects. There were no significant differences among renal function variables (unpublished observations).

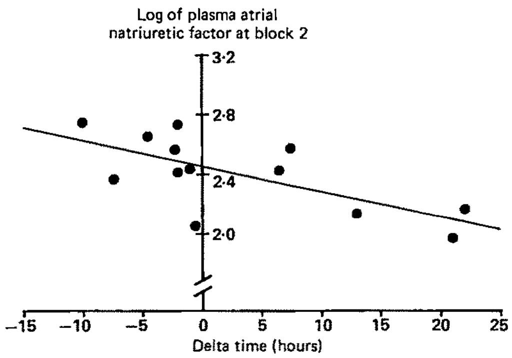

Figure 2 Log of plasma atrial natriuretic factor at block 2 plotted against the difference between the onset of diuresis and the time that the sample of atrial natriuretic factor was taken (delta time). Negative delta time indicates that the sample of atrial natriuretic factor was obtained before the onset of diuresis; positive delta time indicates that atrial natriuretic factor was sampled after onset. Y=2·4371–0·1669 log of plasma atrial natriuretic factor at block 2, r=−0·6892, R^2=0·475, p=0·0092.

All the infants experienced a spontaneous diuresis with a mean onset of 27 (3) hours (range 7 to 43). Figure 2 shows the relationship between delta time and the log of the plasma atrial natriuretic factor concentration during block 2. There is a significant negative correlation (r=−0·69, p=0·0092) between this value and the time between the onset of diuresis and the taking of the atrial natriuretic factor sample during block 2, indicating that atrial natriuretic factor concentrations before the onset of the diuresis were higher than those obtained after the onset.

The onset of diuresis correlated significantly with block 2 F_IO_2 (r=0·63), peak inspiratory pressure (r=0·58), and A–aDO_2 (r=0·63), suggesting that more severe lung disease correlated with a later onset of diuresis. There was no significant correlation between the onset of diuresis and any measured or calculated renal function or variable.

To examine the second hypothesis—that atrial natriuretic factor was associated with maintaining the diuresis until completion—the 37 atrial natriuretic factor measurements from the 13 subjects were correlated with renal and non-renal variables from the coincident block. No significant correlations were found, either by single or multiple regression. Because atrial natriuretic factor may act through a secondary messenger, cyclic guanosine monophosphate,[20] and so have a delayed effect, the same variables measured eight hours later were correlated with the log of the plasma atrial natriuretic factor concentration. Again, no significant relationships were found.

Partial correlation analysis (table 2) showed that there was a significant relationship between urine output and the log of the plasma atrial natriuretic factor (r=−0·44, p<0·01). Urine

Table 2 Relationship between urine output and selected variables by partial correlation analysis

	Correlation coefficient (r)	*p Value*
Birth weight	−0·2733	0·1017
Time after birth	0·2814	0·0916
Fluid intake volume	0·1978	0·2406
Log of plasma atrial natriuretic factor	−0·4412	<0·01
Creatinine clearance	−0·5002	<0·02
Free water clearance	0·8205	<0·0001
Fractional sodium excretion	0·5243	<0·01
Serum sodium concentration	−0·6756	<0·0001
A–aDO_2	−0·6581	<0·0001

volume output was also independently related to renal functions: creatinine clearance ($r=-0{\cdot}50$), free water clearance ($r=0{\cdot}82$), and fractional sodium excretion ($r=0{\cdot}52$). In addition, serum sodium concentration and alveolar arterial oxygen differences were related to urine volume. There were also significant partial correlations between the log of the plasma atrial natriuretic factor concentration and A–aDO_2 ($r=-0{\cdot}63$), serum sodium ($r=-0{\cdot}53$), and free water clearance ($r=0{\cdot}51$) (not listed in table 2).

Discussion

The 13 infants in this investigation began their diuresis half way through the 72 hour study period. The onset of the diuresis coincided with a surge and then fall in the plasma atrial natriuretic factor concentration. In addition, infants who had blood taken for measurement of atrial natriuretic factor concentration before the onset of the diuresis had higher concentrations than those from whom samples were taken at or after the onset of diuresis. Though the results of the present study were consistent with the first hypothesis—that atrial natriuretic factor participates in initiating diuresis in infants with respiratory distress syndrome, they do not suggest that this hormone is a critical factor. If atrial natriuretic factor concentrations were low in infants who failed to achieve an early diuresis, then a more causal relationship could be implied between atrial natriuretic factor and the initiation of diuresis. The current findings may also be consistent with an increase in atrial volume initiating atrial natriuretic factor secretion and diuresis. If this latter interpretation is correct, then the continued diuresis and consequent extracellular volume contraction seen throughout block 3 should have led to a further decline in the atrial natriuretic factor concentration, as was seen in these 13 subjects.

In examining the role of atrial natriuretic factor during the maintenance of diuresis, we could find no correlation between atrial natriuretic factor concentration and any measurement of serum or urine chemistry or calculated renal function during the first 60 hours of life by regression analysis. This lack of correlation may have been the result of using differences in nappy weights and two hour urine collections to estimate renal function, which may not give a true reflection of the underlying renal function. Previous reports, however, have also found no direct and simple relationship between atrial natriuretic factor concentrations and the maintenance of diuresis or renal function.[14 16]

Other studies of the physiology of spontaneous diuresis in newborn infants have found that acute changes in body water distribution,[6] changes in prostaglandin metabolism,[21] changes in glomerular filtration and sodium excretion,[12] and changes in free water clearance,[1] may influence the postnatal diuresis. These were studies of nine to 17 patients each, which were sufficient to isolate the single relationships outlined. Delineating a causal relationship between observed atrial natriuretic factor and urine volume would require over 900 babies to show a significant correlation among these variables, most probably because of the confounding effect of other factors affecting both urine volume and atrial natriuretic factor concentration. Alternatively, partial correlations can be made with a smaller number of subjects.

In the present study partial correlation analysis indicated that there was a significant relationship between urine volume and atrial natriuretic factor concentration during the study period. Significant relationships were found between urine output and creatinine clearance and serum sodium, and we also found that urine output was independent of fluid intake. These findings are consistent with a recent report by Bidiwala *et al.*[12] In addition, this analysis highlighted the reported relationship between urine output and fractional sodium excretion and free water clearance during diuresis, which suggests an underlying change in tubular function.[1]

There was also a significant relationship between the atrial natriuretic factor and A–aDO_2 gradients as well as atrial natriuretic factor and serum sodium. The former is consistent with the findings of Shaffer *et al*, who noted higher atrial natriuretic factor concentrations in infants with more severe respiratory distress syndrome.[14] The latter correlation is consistent with the presumed mechanism of inhibition of atrial natriuretic factor release—that is, the intravascular water volume drops resulting in increased serum sodium concentrations and a fall in the atrial natriuretic factor concentration.

Besides influencing diuresis, there are other potential hypotheses to explain the high atrial natriuretic factor concentrations found in premature infants with respiratory distress syndrome. Hypoxia enhances release of atrial natriuretic factor from the heart, and atrial natriuretic factor may function as a pulmonary vasodilator if there is hypoxic pulmonary vasoconstriction.[22] Alternatively, there may be problems with regulation of atrial natriuretic factor release or end organ effect in the newborn. Both hypoxia and volume infusion increase plasma atrial natriuretic factor concentrations in fetal animals however.[23 24] Brace and Cheung infused pharmacological amounts of atrial natriuretic factor into fetal sheep, and achieved a brisk and prompt diuresis.[25] Changes in intrathoracic pressure from mechanical ventilation may also be a cause of acute rises in atrial natriuretic factor concentrations in infants with respiratory distress syndrome. Application of positive end expiratory pressure in adults, however, leads to a fall in atrial natriuretic factor concentrations.[26]

This study provides evidence in support of both hypotheses. There was a significant rise noted in plasma atrial natriuretic factor concentrations just before and at the onset of diuresis, followed by a fall in the hormone concentration, suggesting that atrial natriuretic factor is necessary for the initiation of postnatal diuresis. It is possible, however, that the two phenomena are coincidental. Like other authors, we found no relationship found between plasma concentrations of the hormone and a number of variables that are causes or consequences of renal function.[14 16] A partial correlation analysis, however, supports the hypothesis that atrial natriuretic factor may contribute to the maintenance physiology of the complete postnatal diuresis. A much larger population needs to be studied to eliminate the effect of confounding variables and accurately determine the relationship between atrial natriuretic factor and postnatal diuresis.

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Association of pneumothorax and hypotension with intraventricular haemorrhage

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Abstract

To test the hypothesis that acute hypotension resulting from pneumothorax would be associated with severe brain injury (grade 3 or 4 intraventricular haemorrhage), 67 very low birthweight (VLBW) infants of 32 weeks' gestation or less with respiratory distress syndrome and pneumothorax were studied. Thirty six had pneumothorax associated with systemic hypotension and 31 had pneumothorax with normal blood pressure. The groups were similar in gestational age and severity of their respiratory distress syndrome. Thirty two of 36 of infants with pneumothorax associated with hypotension (89%) had grade 3 or 4 intraventricular haemorrhage. This percentage was significantly greater than the percentage for infants with pneumothorax and normal blood pressure (three of 31, 10%). The risk ratio for grade 3 or 4 intraventricular haemorrhage for infants with pneumothorax associated with hypotension was 9·8 compared with neonates with pneumothorax and normal blood pressure. These observations are consistent with the hypothesis that systemic hypotension and cerebral hypoperfusion are important factors leading to intraventricular haemorrhage in VLBW infants.

Pulmonary air leak is a common complication in very low birthweight (VLBW) infants, occurring in up to 35% of those being ventilated for respiratory distress syndrome.[1 2] Several reports have indicated that pneumothorax is often associated with, or followed by, intraventricular haemorrhage[3–7] but other studies have not reported an increased risk of intraventricular haemorrhage.[8 9] None of these studies, however, commented on the severity of symptoms caused by the pneumothorax or whether the pneumothorax was accompanied by systemic hypotension. A small pneumothorax may be asymptomatic or mildly symptomatic, but if the pneumothorax is associated with appreciably raised intrathoracic pressure then cardiac filling, cardiac output, and systemic blood pressure will fall.[10–12] If this happens cerebral infarction is seen as the primary event, with intraventricular haemorrhage not occurring until after the systemic blood pressure has been raised to, or above, normal levels.[11 12]

In this study we tested the hypothesis that a pneumothorax with systemic hypotension would increase the likelihood of severe intraventricular haemorrhage in VLBW infants being ventilated for respiratory distress syndrome. Episodes of pneumothorax after which the blood pressure remained normal would be less likely to result in severe intraventricular haemorrhage.

We studied the incidence of grades 3 and 4 intraventricular haemorrhage among VLBW infants with pneumothorax that had caused hypotension, and compared it with the incidence of intraventricular haemorrhage in infants with pneumothorax and normal blood pressure.

Patients and methods

We retrospectively identified 82 infants from the records of our neonatal intensive care unit who were admitted between 1 January 1983 and 31 December 1986, were of 32 weeks' gestation or less, required mechanical ventilation for respiratory distress syndrome, and developed a pneumothorax. Fifteen were excluded from the study: five with hypoplastic lungs, one in whom the pneumothorax occurred as a terminal event, one in whom the pneumothorax was secondary to a thoracotomy for ligation of a patent ductus arteriosus, and two with congenital defects of the central nervous system. In addition, six others were excluded because they did not have a cranial ultrasound scan carried out after their pneumothorax, or because they had not undergone necropsy to see if there was an intraventricular haemorrhage.

The remaining 67 infants were studied. Two of the authors (DM, CWG) reviewed each neonate's chart to find out if the pneumothorax was associated with systemic hypotension. Blood pressure was monitored continuously by a transducer attached to an indwelling umbilical arterial catheter. Systemic hypotension, defined as a sudden fall in the mean blood pressure to less than two standard deviations below the mean for age (30 mm Hg or less,[13]) resulted from a pneumothorax in 36 infants. An additional 31 infants had a pneumothorax but did not develop hypotension. Cranial ultrasound scans were independently scored according to the Papile system by a radiologist and a neonatologist (AEK) who did not know the medical history.[3] The most severe grade of intraventricular haemorrhage on any ultrasound scan was used for the infant's score. For infants who died (n=4) before ultrasound examination, the severity of intraventricular haemorrhage was determined at necropsy.

For each infant we recorded birth weight, sex, race, gestational age, Apgar score at one and five minutes, obstetric complications, time of first pneumothorax, and ventilator settings both at 12 hours of age and immediately before the first pneumothorax. The total number of

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days on the ventilator and being treated with oxygen, and the mortality, were also noted.

The incidence of intraventricular haemorrhage was determined for each group. Data were compared by the χ^2 test and the unpaired Student's *t* test. The relative risks for intraventricular haemorrhage for each group were calculated to answer the following question: is pneumothorax with systemic hypotension associated with an increased incidence of grades 3 and 4 intraventricular haemorrhage compared with pneumothorax during and after which the blood pressure remains normal?

Results

Although the infants in the two groups were of similar gestational age (28·6 (1·8) weeks compared with 29·1 (2·2) weeks) the mean birth weight of the hypotensive infants (1026 (293) was lower than that of the group with normal blood pressure (1250 (356) g, p<0·01) (table 1). In addition there were more boys in the hypotensive group (25 of 36, 69%) than in the group with normal blood pressure (15 of 31, 42%) (p<0·03).

The average age of occurrence of the first pneumothorax was 29 hours (range 4–127) and 32 hours (range 2–100) in the hypotensive and normotensive groups, respectively. The pneumothorax was bilateral in about half the infants in each group; pneumothorax was right sided in about 66% of the unilateral pneumothoraces in each group.

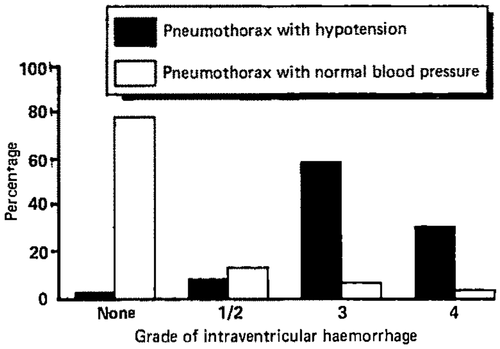
Mean baseline measurements of blood pressure before the pneumothoraces were similar in the two groups (table 2). In all the infants who became hypotensive the mean arterial pressure fell when the pneumothorax occurred from 40 (7·1) mm Hg to 19·2 (10·1) mm Hg (p<0·001). Mean blood pressures did not change significantly during the pneumothorax in the normotensive group.

After the pneumothorax the arterial oxygen tension fell significantly (from 9·73 kPa to 7·07 kPa, p<0·05) and the arterial carbon dioxide tension rose (from 4·80 kPa to 6·67 kPa, p<0·05) in the hypotensive infants, but did not change significantly in the normotensive infants (from 8·66 kPa to 8·13 kPa and from 5·33 kPa to 6·00 kPa, respectively).

There were no significant differences between the groups in ventilator mean airway pressure at 24 hours of age, but a significantly higher fractional inspiratory oxygen (F_IO_2) was required in the hypotensive infants (0·75 compared with 0·62, p<0·05). There was no significant difference between the groups in mean airway pressure just before pneumothorax.

RELATIONSHIP BETWEEN INTRAVENTRICULAR HAEMORRHAGE AND PNEUMOTHORAX

The incidence of intraventricular haemorrhage for each study group is shown in the figure. Only one infant (3%) in the hypotensive group had a normal cranial ultrasound scan compared with 24 infants (77%) in the group with normal blood pressure. Thirty two infants, 89% of those in the hypotensive group, had grade 3 or 4 haemorrhages. The increased incidence of grade 3 or 4 intraventricular haemorrhage in this group of infants with pneumothorax and hypotension is highly significant compared with the group whose blood pressure remained normal (3 of 31, 10%, p<0·01). The relative risk of grade 3 or 4 intraventricular haemorrhage was 9·8 for



*Infants with pneumothorax and hypotension had a higher incidence of grade 3 and 4 intraventricular haemorrhage. (*p<0·01).*

Table 1 Clinical characteristics of the study groups

	Pneumothorax with hypotension (n=36)	*Pneumothorax with normal blood pressure (n=31)*	*p Value*
Mean (SD) birth weight (g)	1026 (293)	1250 (356)	<0·01
Mean (SD) gestational age (weeks)	28·6 (1·8)	29·1 (2·2)	0·3
Mean Apgar scores at 1 min/5 min	3/5	3/5	
No (%) boys	25 (69)	15 (48)	0·07
No (%) black infants	15 (42)	18 (58)	0·6
No (%) born in hospital	22 (61)	21 (68)	0·6
No (%) vaginal births	24 (67)	12 (39)	0·02
No (%) with breech presentation	6 (17)	6 (19)	0·8
No (%) with rupture of membranes for ≥24 hours	6 (17)	5 (16)	0·9
No (%) with respiratory distress syndrome grade 3 or 4	21 (58)	13 (42)	0·2

Table 2 Mean (SD) arterial blood pressure (mm Hg)

	Before pneumothorax	*During pneumothorax*	*After recovery of pneumothorax*
Pneumothorax with hypotension	40·0 (7·1)*	19·2 (10·1)*	37·9 (7·8)
Pneumothorax with normal blood pressure	36·8 (4·8)	36·3 (4·7)	37·3 (4·3)

*p<0·001.

infants who became hypotensive compared with those whose blood pressure remained normal.

Because the study was retrospective we were not able to control for the timing of the cranial ultrasound scans. We therefore cannot say whether the pneumothorax preceded the intraventricular haemorrhage in all cases. Nevertheless, 17 infants in the hypotensive group had cranial ultrasound scans carried out both before, and within 24 hours after, their pneumothorax. Before the pneumothorax 10 of these 17 infants had normal cranial ultrasound scans and seven had either a grade 1 or grade 2 intraventricular haemorrhage. On repeat cranial ultrasound examination of the same infants after the pneumothorax, none had a normal cranial ultrasound, one had a grade 1–2 intraventricular haemorrhage, and 16 had grade 3 or 4 intraventricular haemorrhages. Though we cannot be certain that pneumothorax with a fall in blood pressure preceded the intraventricular haemorrhage in all cases, we believe that the observation in these 17 infants make it likely that severe intraventricular haemorrhage followed the development of pneumothorax.

MORTALITY AND MORBIDITY

Mortality was significantly higher in the hypotensive group (15 of 36, 42% compared with 3 of 31, 10%; $p<0{\cdot}005$). Among the surviving infants, there was no difference between groups in the length of time the infants received assisted ventilation or supplemental oxygen. Residual brain damage was more common among the surviving hypotensive infants compared with the infants whose blood pressure remained normal; nine of 36 (25%) compared with none of three of survivors developed unilateral periventricular leucomalacia with porenchephaly ($p<0{\cdot}005$), and 19 of 36 (53%) compared with one of 31 (3%) developed ventriculomegaly ($p<0{\cdot}01$).

Discussion

Intraventricular haemorrhage occurs in about 35% of premature neonates weighing less than 1500 at birth, and is a serious cause of mortality and morbidity.[3] In addition, one recent report showed a significant association between hypotension and cerebral lesions or death.[12] Intraventricular haemorrhage originates in the capillary network of the germinal layer, which is highly vascular and poorly supported. The pathogenesis of intraventricular haemorrhage is complex, but its occurrence is greatest in VLBW infants with respiratory distress syndrome.[14]

A close association between pneumothorax and the occurrence and extension of intraventricular haemorrhage has been reported previously by Dykes *et al* who found that if a premature infant had an alveolar rupture, the risk of intraventricular haemorrhage was increased 2·5-fold compared with similar infants without alveolar rupture.[5] Of all the risk factors studied, they found that the presence of pneumothorax had the strongest association with the later development of intraventricular haemorrhage. Lipscomb *et al*,[4] Hill *et al*,[6] and Thorburn *et al*[15] also reported a close association between the development of a pneumothorax and a later intraventricular haemorrhage. Cooke,[8] and Van De Bor *et al*,[9] however, did not find an increased incidence of intraventricular haemorrhage in premature infants with pneumothorax. The apparent discrepancy among these previous studies might be caused by differences in the severity of the pneumothoraces in the populations studied.

Pneumothorax in an infant can be virtually asymptomatic or may be associated with severe circulatory disturbances including hypotension and hypoperfusion. When severe pneumothorax leads to inadequate cardiac filling and systemic hypotension (air block syndrome) cerebral ischaemia may be induced, with the arterial watershed zones in the periventricular regions of the brain being particularly prone.[11]

Published data about the effect of pneumothorax on arterial blood pressure are somewhat conflicting. Hypotension secondary to pneumothorax has been clearly shown in both animal and human studies.[2 12 16–19] Other studies, however, have reported either no change in the arterial blood pressure or an increase in the arterial blood pressure with pneumothorax.[6 20] It is likely that the effect of pneumothorax on arterial blood pressure in both animals and humans can be explained by the difference in the severity of the pneumothoraces studied. When there is sufficient intrathoracic pressure to compress the intrathoracic vessels severely, systemic hypotension will result (air block syndrome).

Our study has shown that 89% of our 36 infants with pneumothorax resulting in systemic hypotension developed grade 3 or 4 intraventricular haemorrhage. This percentage was significantly greater than for infants with pneumothorax that was not associated with hypotension (9%). There was also a higher mortality among the infants with pneumothorax and hypotension than among infants with pneumothorax but no fall in blood pressure (42% compared with 10%, $p<0{\cdot}005$). In addition, infants with pneumothorax resulting in hypotension had a higher incidence of periventricular leucomalacia with porencephaly (25% compared with 0%, $p<0{\cdot}01$) and ventricular dilation (53% compared with 3%, $p<0{\cdot}01$). The development of periventricular leucomalacia and ventricular dilatation in these infants is consistent with them having experienced an episode of severe cerebral ischaemia or infarction, or both.

One possible problem with this comparison is that the infants with pneumothorax associated with hypotension had a lower mean birth weight and there was a preponderance of boys. The groups were of similar gestational age, however, and the severity of their respiratory distress syndrome was similar (as shown by similar mean airway pressures on assisted ventilation and similar findings on chest radiographs. We are unable to say definitively that their higher incidence of grade 3 and 4 intraventricular haemorrhage is solely the result of their pneumothorax with associated hypotension. Nevertheless, those infants who developed a pneumothorax with hypotension had an extremely high incidence of intraventricular haemorrhage (89%), identifying them as a group at extreme risk. No other single factor or combination of risk factors has been as strongly predictive of severe intraventricular haemorrhage. We therefore believe that these results strongly suggest (but cannot prove directly) that the pneumothorax associated with hypotension was the cause of the haemorrhage.

These observations support the theory that cerebral hypoperfusion or ischaemia precedes development of severe intraventricular haemorrhage.[11] Recent reports indicate that premature infants who develop hypotension in the first days of life are likely to have cerebral parenchymal injury or severe intraventricular haemorrhage, while infants of similar gestational age who are not hypotensive do not develop these injuries.[11] [12] These infants lack cerebral autoregulation so that hypotension results directly in cerebral hypoperfusion.[11] We believe it is possible that the cerebral hypoperfusion that accompanies the systemic hypotension causes infarction of both the periventricular white matter and the germinal matrix. Later, when the blood pressure and cerebral blood flow are raised to normal values, the germinal matrix capillaries rupture and germinal matrix or intraventricular haemorrhages develop.

In summary, we found that 89% of 36 VLBW infants with respiratory distress syndrome who developed a pneumothorax with hypotension also developed a grade 3 or 4 intraventricular haemorrhage. These severe degrees of intraventricular haemorrhage have been associated with early mortality or neurological handicap in survivors. Based on our results, additional prospective studies should be carried out to determine the incidence and severity of brain injury in VLBW infants after episodes of moderate and severe hypotension.

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Increased incidence of respiratory distress syndrome in babies of hypertensive mothers

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Abstract

There is controversy over the effect of hypertension in pregnancy on the incidence of neonatal respiratory distress syndrome. We investigated the association between maternal hypertension and the incidence of respiratory distress syndrome in 268 very low birthweight babies of less than 34 weeks' gestation.

A lower incidence of respiratory distress syndrome was associated with growth retardation and membrane rupture >24 hours. Maternal hypertension was associated with an increased incidence of respiratory distress syndrome. We used the multiple logistic regression model to control for confounding variables, as the maternal and neonatal factors associated with respiratory distress syndrome were not evenly distributed between the two groups.

After adjustment for birth weight, gestational age, growth retardation, and membrane rupture >24 hours, the risk of developing respiratory distress syndrome was significantly greater in babies of hypertensive mothers. Significance was lost when labour before delivery and mode of delivery were taken into account. The increased incidence of respiratory distress syndrome in babies of hypertensive mothers may be due to the absence of labour before delivery because of the greater likelihood of caesarean section.

The effect of hypertension in pregnancy on the incidence of neonatal respiratory distress syndrome remains controversial. A number of studies have supported the widely accepted view that maternal hypertensive disease protects against the development of respiratory distress syndrome.[1–3] Some workers have found an increase in the incidence of respiratory distress syndrome,[4 5] however, and others no change in the incidence[6] among babies born to hypertensive mothers. Most of these studies have involved small numbers of subjects and not all have attempted to adjust for confounding variables. We investigated the association between maternal hypertension and the incidence of respiratory distress syndrome in a large group of very low birthweight babies (birth weight ≤1500 g) of less than 34 weeks' gestation.

Patients and methods

This study was performed in the Royal Maternity Hospital, Belfast, which is a high risk, university based obstetric unit, having approximately 4000 deliveries per year. Many of these are referred from other centres in Northern Ireland for specialist perinatal care. The hospital has a neonatal unit with provision for seven intensive care and 11 special care cots.

We used an established database of information on more than 600 liveborn babies with birth weight ≤1500 g who were managed in Royal Maternity Hospital from 1978 to 1988. Using this, we first excluded all babies of 34 weeks' gestation or greater, whose risk of developing respiratory distress syndrome was likely to be low. From the remainder we identified all babies (n=134) who had been born to mothers who had hypertension in pregnancy (diastolic blood pressure persistently greater than or equal to 90 mm Hg).[7]

A group of 134 babies also ≤1500 g birth weight and <34 weeks' gestation, born to normotensive mothers, was used for comparison. These were randomly selected from the database, matching only for year of birth to allow for the effects of improved outcome associated with the development of newer forms of treatment.

Information on mothers and their babies was obtained from review of patient hospital records. We recorded the following maternal and neonatal factors: presence of labour before delivery, mode of delivery, membrane rupture >24 hours, antenatal steroid administration, infant's sex, birth weight, gestational age, and growth retardation (birth weight less than 10th centile for gestational age). Infant gestation was based upon menstrual dates, early ultrasound scans where performed, and clinical judgment by medical staff in the neonatal unit. Respiratory distress syndrome was defined as the presence of tachypnoea >60/minute, sternal recession and expiratory grunting, need for supplemental oxygen, and a radiological picture of diffuse reticulogranular shadowing with an air bronchogram.[8] The severity of respiratory distress was judged by maximum fraction of inspired oxygen required, need for mechanical ventilation, and presence of grade 3/4 radiographic changes.[9] Information on lecithin-sphingomyelin ratios was available in only 28% of cases and was not used as part of our definition of respiratory distress syndrome.

Preliminary statistical analyses were performed using the Z, χ^2, and Mann-Whitney U tests for independent samples. Significance levels, where quoted, are for two tailed tests. We used the multiple logistic regression model to study the association between maternal hypertension and the incidence of respiratory distress syndrome, controlling for the confounding effects of other variables.

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Results

Maternal and neonatal factors associated with respiratory distress syndrome are shown in tables 1 and 2. Babies who developed respiratory distress syndrome were of significantly lower birth weight and gestational age than those who did not. A significantly lower incidence of respiratory distress syndrome was associated with membrane rupture >24 hours and growth retardation. Antenatal steroid administration, presence of labour before delivery, delivery by caesarean section, and male sex were not associated with a difference in the incidence of respiratory distress syndrome; it was significantly more common in babies born to hypertensive mothers (table 3).

We determined the distribution of these factors within the two study groups (table 3). Babies in the hypertensive group had a mean gestational age two weeks greater than the normotensive group but had a similar mean birth weight. All cases of membrane rupture >24 hours occurred in the normotensive group. Most of the normotensive mothers had vaginal deliveries whereas most hypertensive patients were delivered by caesarean section, a small number after a preceding period of labour. A greater proportion of growth retarded babies came from the hypertensive group. There was no difference in the proportion of boys or incidence of antenatal steroids.

We performed multivariate analysis using the

Table 1 Incidence of maternal and neonatal factors in relation to the occurrence of respiratory distress syndrome: hypertensive group (n=134)

	Respiratory distress syndrome (n=87)	*No respiratory distress syndrome (n=47)*	*p Value*
Mean (SD) gestation (weeks)	29·7 (2·0)	31·4 (1·5)	<0·0001
Mean (SD) birth weight (g)	1093 (234)	1229 (214)	<0·001
No (%) with membrane rupture >24 hours	0	42 (89)	0·0001
No (%) undergoing labour	8 (9)	9 (19)	NS
No (%) having caesarean section	80 (92)	42 (89)	NS
No (%) with growth retardation	33 (38)	34 (72)	<0·001
No (%) having antenatal steroids	13 (15)	7 (15)	NS
No (%) boys	34 (39)	19 (40)	NS

Table 2 Incidence of maternal and neonatal factors in relation to the occurrence of respiratory distress syndrome: normotensive group (n=134)

	Respiratory distress syndrome (n=69)	*No respiratory distress syndrome (n=65)*	*p Value*
Mean (SD) gestation (weeks)	27·6 (2·4)	29·2 (2·2)	<0·0001
Mean (SD) birth weight (g)	1083 (259)	1250 (219)	<0·0001
No (%) with membrane rupture >24 hours	12 (17)	30 (46)	<0·001
No (%) undergoing labour	56 (81)	55 (85)	NS
No (%) having caesarean section	20 (29)	13 (20)	NS
No (%) with growth retardation	4 (6)	13 (20)	<0·05
No (%) having antenatal steroids	10 (14)	14 (22)	NS
No (%) boys	34 (49)	31 (48)	NS

Table 3 Distribution of maternal and neonatal factors within the study groups

	Hypertensive (n=134)	*Normotensive (n=134)*	*p Value*
No (%) with respiratory distress syndrome	87 (65)	69 (51)	<0·05
Mean (SD) gestation (weeks)	30·3 (2·0)	28·4 (2·4)	<0·0001
Mean (SD) birth weight (g)	1140 (236)	1164 (254)	NS
No (%) with membrane rupture >24 hours	0	42 (31)	<0·0001
No (%) undergoing labour	17 (13)	111 (83)	<0·0001
No (%) having caesarean section	122 (91)	33 (25)	<0·0001
No (%) with growth retardation	67 (50)	17 (13)	<0·0001
No (%) taking steroids	20 (15)	25 (19)	NS
No (%) boys	53 (40)	70 (52)	NS

Table 4 Odds for babies of hypertensive mothers developing respiratory distress syndrome relative to babies of normotensive mothers

Adjusted for:	*Relative odds of respiratory distress syndrome*	*95% Confidence intervals*	*Likelihood ratio χ^2 (df=1)*
No factors	1·7	1·1 to 2·9	4·99*
Birth weight, gestation	3·7	1·9 to 7·3	15·79**
Birth weight, gestation, growth retardation	3·8	1·9 to 7·6	15·43**
Birth weight, gestation, growth retardation, membrane rupture >24 hours	2·3	1·1 to 4·9	5·06*
Birth weight, gestation, growth retardation, membrane rupture >24 hours, labour	1·4	0·6 to 3·2	0·54
Birth weight, gestation, growth retardation, membrane rupture >24 hours, delivery	1·6	0·7 to 3·7	1·16
Birth weight, gestation, growth retardation, membrane rupture >24 hours, labour, delivery	1·4	0·6 to 3·2	0·46

*p<0·05, **p<0·001.

*Table 5 Incidence and severity of respiratory distress syndrome where present**

	Hypertensive (n=87)	*Normotensive (n=69)*
No (%) with grade 3/4 radiographic changes	55 (63)	47 (68)
No (%) needing mechanical ventilation	66 (76)	56 (81)
Mean (SD) maximum fraction of inspired oxygen	0·62 (0·24)	0·68 (0·24)

*There were no significant differences in the variables between the hypertensive and normotensive groups.

multiple logistic regression model to investigate further the association between hypertension and respiratory distress syndrome, adjusting for the confounding effects of gestational age, birth weight, growth retardation, and membrane rupture >24 hours. After this adjustment, there was still a significant association between maternal hypertension and respiratory distress syndrome (table 4). However, when mode of delivery and/or the presence of labour before delivery were also included in the model the association was no longer significant.

Severity of respiratory distress, as judged by radiographic changes, maximum fraction of inspired oxygen, and need for mechanical ventilation was similar in both hypertensive and normotensive groups (table 5). Babies in the hypertensive group who developed respiratory distress syndrome had a significantly greater survival rate (67/87, 77%) than the normotensive group (37/69, 54%).

Discussion

Although it is commonly stated that maternal hypertension is protective against the development of respiratory distress syndrome,[10] the evidence for this is conflicting.[1–6] As many factors affect the incidence of respiratory distress syndrome it is important to control for the influence of these when assessing the effect of a single variable, such as maternal hypertension. Most studies have involved small numbers of patients and some have not controlled for the effect of confounding variables.

Respiratory distress syndrome was significantly more common in babies of hypertensive mothers before correction for confounding variables (65% compared with 51%). After adjustment for confounding variables the incidence of respiratory distress syndrome remained higher in the hypertensive group, until mode of delivery and labour before delivery were taken into account. These two factors are consequences of maternal hypertension, in that pre-eclampsia often leads to emergency caesarean section without a preceding period of labour. Respiratory distress syndrome is more common after hypertensive pregnancies but the reason may simply be that the incidence of caesarean section is increased and a period of labour before delivery before birth is reduced. Alternatively, caesarean section and absence of labour may simply be acting as markers for hypertension. The available data did not allow us to distinguish between these alternatives.

There was no difference in the severity of respiratory distress syndrome between the two groups, though mortality was lower in babies in the hypertensive group who developed respiratory distress, perhaps due to the significantly greater mean gestational age of these babies (table 3).

This study supports other evidence to suggest that respiratory distress syndrome is more and not less common in babies of hypertensive mothers.[4 5] Little information on this subject exists in the literature. More research is therefore needed, preferably in the form of a large randomised controlled trial to determine whether different policies for labour and delivery of hypertensive mothers are associated with significant differences in the incidence of respiratory distress syndrome in their babies.

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Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity

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Abstract

A total of 121 infants who required indomethacin for persistent ductus arteriosus in Liverpool and Cambridge over a four year period were randomised to receive either 0·1 mg/kg daily for six days or 0·2 mg/kg every 12 hours for three doses. The groups were of similar birth weight and gestational and postnatal age, though those treated with a low dose were by chance receiving a higher percentage of oxygen at the start of treatment and there were more deaths from bronchopulmonary dysplasia in this group. Of 59 infants treated with the prolonged course 53 (90%) responded initially to indomethacin compared with 48 of 62 (77%) treated conventionally—a difference of 13% (95% confidence interval for the difference 0 to 26%). Of the 53 responders 11 (21%) relapsed after low dose indomethacin, whereas after the shorter course 19 of 48 (40%) relapsed. This difference was significant (95% confidence intervals 3 to 37%). Side effects, mainly gastrointestinal haemorrhage, were similar in both groups. Significantly fewer infants experienced a rise in serum creatinine or urea concentration after treatment with low dose indomethacin. A prolonged low dose course of indomethacin offers advantages over conventional treatment.

Several double blind trials have shown that indomethacin is capable of reducing left to right shunt through a persistent ductus arteriosus in preterm infants.[1 2] The success rate after treatment is between 60 and 80%, with a relapse rate of about 30%.[3–5] The observation that infants treated at greater postnatal age seemed to respond less well,[6] resulted in studies of early treatment either as prophylaxis given to a cohort on the basis of birth weight,[7–9] or after identification of shunting with an early aortogram or contrast echocardiography.[10 11] Prophylactic indomethacin reduced subsequent ductal shunting, but as only 30% of a very low birthweight cohort develop an important left to right shunt, many would consider that the risk of side effects outweighs any potential benefit. Early treatment (at a mean of 2·9 days, as soon as any clinical signs were detected) was associated with a reduction in the amount of oxygen needed by those weighing less than 1000 g in one study,[12] but this has not always been confirmed and one small trial has recently shown the opposite.[13]

Pharmacokinetic studies have also been used in attempts to improve the response to indomethacin. These have shown that the absorption is erratic after enteral administration,[14] and that even after an intravenous dose plasma concentrations vary 20-fold and overwhelm any differences in half life and clearance related to postnatal and gestational age.[15] In general the response of the ductus and the side effects of indomethacin do not correlate well with the plasma indomethacin concentration.[16 17] Brash *et al* proposed a threshold of 250 ng/ml and noted that relapse occurred on about the fifth day when concentrations of indomethacin had fallen to about 50 ng/ml.[15] Seyberth *et al* used on line monitoring, and thought that a plasma concentration of 1000 ng/ml may be needed for as long as a week.[18] Our previous work showed, however, that five of the seven infants who had gastrointestinal bleeds were among the seven with concentrations above 1000 ng/ml at any time.[7] In further trials Seyberth *et al* have initiated treatment starting with indomethacin concentrations of 1000 ng/ml and continuing at 150–750 ng/ml.[19]

Inhibition of prostaglandin synthesis can be achieved even with low plasma concentrations of indomethacin in the newborn,[7] as well as in adults.[20] This may explain the poor correlation between response and plasma concentrations. Both plasma and urinary prostaglandin synthesis returns about five days after indomethacin has been stopped,[7 21] corresponding to the time at which indomethacin concentrations are falling and possibly thereby contributing to failure of treatment. These results have led to trials of prolonged low dose indomethacin,[22 23] which appears to be safe.[18] In the study we compared prolonged low dose indomethacin with three higher doses at intervals of 12 hours in infants requiring treatment for left to right shunt due to persistent ductus arteriosus that had been diagnosed clinically.

Patients and methods

Babies weighing less than 2500 g at birth who developed clinical signs of persistent ductus arteriosus that required treatment with indomethacin were enrolled in Liverpool and Cambridge. Treatment was allocated by opening a sealed envelope randomising the baby to receive either a six day course of 0·1 mg/kg or three doses at intervals of 12 hours of 0·2 mg/kg. The course was completed unless treatment was stopped because of a complication. Information on the subsequent course was collected prospectively; relapse was defined as a recurrence of systolic murmur and increased pulse volume. Between September 1985 and July 1989, 123 babies were enrolled; one was excluded because of a diagnosis of hydrops fetalis, and another because the course was stopped after an incorrect prescription of 1·0 mg/kg. The trial was approved by the ethics committees of both hopitals.

POWER

The study design allowed us to examine two end points: response to treatment and relapse after treatment. From the results of previous work, about 70% of babies could be expected to respond to indomethacin with a relapse rate of 30%.[4 7] Assuming that an improvement in the response rate to 90% might occur, a formula was used to calculate numbers.[24] Calculating the formula for alpha=0·05—that is, for a 5% chance of rejecting the null hypothesis and detecting a difference in treatments when none exists—and beta=0·2—giving a 20% chance of committing a type II error and failing to detect a true difference—a total of 122 babies would be needed. The power of the study with this number of babies would be 80%. A similar calculation using the sample size tables of Fleiss[25] results in a total of 142 babies for 80% power, but Pocock[26] has pointed out that these tables are designed for the analysis to be done using χ^2 with Yates's correction and that if this is not necessary then the numbers are an overestimate.

For the end point of relapse, in order to detect a reduction in the relapse rate from the expected figure of 30% to 15% with 80% power 192 babies would be needed: 122 babies gives only 65% power, and therefore a 35% chance of failing to detect a true difference.

STATISTICAL ANALYSIS

To analyse the results we used the statistical package for the social sciences (SPSS).[27] The χ^2 test was used for comparison of groups, and Student's *t* test or the Mann-Whitney U test where appropriate. Results are also reported with calculation of 95% confidence intervals (CI) as suggested by Gardner and Altman.[28]

Results

RESPONSE AND RELAPSE

The treatment groups were well matched for birth weight and gestational age, and there were no differences between centres or in the postnatal age at which the babies received treatment (table 1). Of 59 babies, 53 responded to the low dose course (90%) compared with 48 of 62 (77%) after a conventional course (table 2). This represents a treatment difference of 13% with (95% CI 0 to 26%, χ^2 4·32, p=0·06). Eleven of the 53 babies who responded to the prolonged course subsequently relapsed (21%) compared with 19 of 48 after the conventional course (40%); the difference between treatments was 19% (95% CI 3 to 37%, χ^2=4·28, p<0·05). Three of these babies required ductal ligation. The results are shown graphically in the figure, together with the treatment differences and 95% CI for the other clinically relevant outcomes.

SIDE EFFECTS

There was no significant difference in side effects recorded during the administration of indomethacin, with 10 and 13 babies, respectively, experiencing any side effect that was possibly due to treatment; most of these were gastrointestinal haemorrhages. Treatment was stopped in a total of eight babies: two had gastrointestinal perforations after a conventional course of treatment and required ductal ligation because of treatment failure; six had

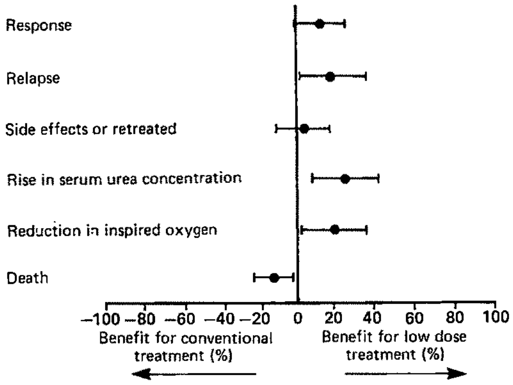
Table 1 Comparison of 59 babies treated with prolonged low dose of indomethacin and 62 treated with conventional dose

	Indomethacin		*Statistical test*	*p Value*
	0·1 mg/kg×6 (low dose)	*0·2 mg/kg×3 (conventional dose)*		
Mean (SD) birth weight (g)	1116 (340)	1135 (340)	*t* Test	0·71
Mean (SD) gestational age (weeks)	27 (2·2)	27 (2·2)	*t* Test	0·72
Centre:				
Liverpool	23	32	χ^2	0·2
Cambridge	36	30		
Time treated:				
Postnatal age <7 days	32	39	χ^2	0·43
Postnatal age ≥7 days	27	23		
Median (interquartile range) maximum oxygen concentration day 1	40 (30–60)	30 (25–45)	Mann-Whitney	0·01

Table 2 Outcome after treatment with either prolonged low dose of indomethacin (n=59) or conventional course (n=62). Results are given as number (%) of babies

	Indomethacin		χ^2	*p Value*
	0·1 mg/kg×6 (low dose)	*0·2 mg/kg×3 (conventional dose)*		
Response	53 (90)	48 (77)	3·37	0·06
Relapse	11 (21)	19 (40)	4·28	0·04
Retreated	10 (19)	11 (23)	0·25	0·62
Side effects	10 (17)	13 (21)	0·32	0·57
Rise in serum urea or creatinine concentration	17 (29)	33 (53)	6·68	0·009
Reduction in inspired oxygen at 6 days	34 (68)	21 (34)	6·60	0·009
Died	10 (17)	3 (5)	4·62 (3·44)*	0·03 (0·06)*

*These results are with (and without) Yates's correction.



Differences in treatment and 95% confidence intervals of differences in outcomes.

bleeding complications; and two went into acute renal failure (short course). Significantly fewer babies had any rise in serum urea or creatinine concentrations after treatment with the low dose regimen: 29% compared with 53% (χ^2 6·68, p=0·009) (table 2).

DEATHS

There were significantly more deaths after the long course: 10 of 52 (17%) compared with three of 62 (5%) (p=0·03). Only two of the deaths occurred during the first month of life. One was after intensive care had been withdrawn because of periventricular leucomalacia and periventricular haemorrhage in a severely ill baby, and the second was due to persistent pulmonary hypertension, possibly related to showers of platelet emboli (seen at necropsy) from a umbilical catheter that was rather high. This baby had received only one dose of indomethacin, as the platelet count fell rapidly over the first few days. Five of the remaining eight deaths in the long course group were at several months of age of bronchopulmonary dysplasia, the remaining three being from sepsis at about 1 month of age. The remaining deaths in the short course group were due to a late cot death and bronchopulmonary dysplasia. Thus no deaths could be directly attributed to treatment, and the higher incidence of deaths from bronchopulmonary dysplasia in the group receiving the long course may reflect the fact that the babies were receiving a significantly higher percentage of oxygen at the start of treatment: median 40% (interquartile range 30 to 60%) and 30% (25 to 45%).

SUBGROUP INFORMATION

Analysing subgroups of babies treated at less than or greater than one week postnatal age and who were less than or greater than 28 weeks' gestation or weighed less than 1000 g also showed no significant differences in outcome. Initial response to treatment was between 68% and 92%, the best response being in babies of less than 1 week postnatal age treated with a long course. A good response was also achieved, however, at a postnatal age of greater than 1 week in 39 babies. Babies of gestational age less than 28 weeks or birth weight less than 1000 g responded well to treatment without the increase in side effects described in some studies.

Discussion

Relapse after functional closure of the persistent ductus arteriosus with indomethacin has been a problem since the early days. Attempts at limiting side effects have resulted in a reduction of the dose by some 10-fold from that used originally in the newborn and prescribed for adult patients.[29] Indomethacin is an extremely powerful prostaglandin synthetase inhibitor and because prostaglandins are widely distributed and involved in the control of the microcirculation throughout the body the drug has widespread effects. Perhaps the most important of these in preterm babies are those regulating the renal and cerebral circulations. Studies examining the effect of indomethacin on cerebral blood flow velocity have consistently shown a reduction.[30 31] Although some workers have suggested that this may be of benefit in the prophylaxis of periventricular haemorrhage,[32] this is not a consistent finding.[33] Few long term follow up studies have been reported: low cerebral blood flow may be detrimental in the immediate postpartum period. Most of the evidence, therefore, is against the use of prophylactic indomethacin and more studies of the type reported here are needed in order to establish the best timing, duration, and dose, if the drug is to be used effectively in a 'rescue' fashion.

In this study we examined the effects of the same total dose of indomethacin given in two different ways. There was a trend towards an improvement in the initial response rate after the prolonged course, with 95% CI for the difference in response compared with a conventional short course falling between no fewer responses and 25% more closures. The high relapse rate often reported after indomethacin probably results from a resurgence of prostaglandin synthesis and makes prolonged treatment logical.[7 21] The results showed a significant difference in relapse rate although the risk of a type II error was high. Few of the relapses noted in this study were thought to be important enough to require retreatment or to require an increase of ventilatory support.

The increase in mortality after a prolonged course has not been reported before, and although it was probably explained by the highly significant difference in inspired oxygen concentration at the start of treatment in this group, the observation reminds us of the need to evaluate new treatments carefully and to sound a note of caution. The concern about impaired renal function in babies receiving prolonged indomethacin has not been supported by this study—in which there were fewer babies who experienced a rise in serum creatinine or urea concentrations after treatment—or by other work.[18] Relatively large numbers of infants weighing less than 1000 g at birth were treated, and responded equally well to indomethacin as those of higher birth weights.

Prolonged low dose indomethacin offers an alternative effective way of achieving reduction of left to right shunt in babies in whom a clinical diagnosis of persistent ductus arteriosus has been made. Prolongation of treatment improves the initial response and reduces the relapse rate.

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Light transmission measurements and phototherapy eyepatches

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Abstract

The transmission characteristics of phototherapy eyeshields have been measured under conditions that mimic the clinical situation. Peak transmission (<10%) was detected at 700 nm for the poorest patch tested and <2% for either of the other patches examined. The optics of measurement systems are considered with reference both to this and previous studies of light transmission through eyepatches. The simplicity and effectiveness with which eyepatches can be secured may be as important as their transmission characteristics.

It is routine clinical practice to protect the eyes by covering them with patches while neonates are being treated by phototherapy. As the intensity of light produced by such phototherapy units is in the region known to cause retinal damage in animals the light attenuating properties of eyeshields are of clinical interest.[1]

There are several studies that have measured the transmission of light through commercial phototherapy eyeshields and/or 'home made' patches used in some neonatal units.[2–4] These may be criticised on two main grounds: firstly the instruments used could not obtain spectral plots,[2 4] and secondly the relative positions of the light source, eyepatch, and detector did not mimic the clinical situation.[3]

Porat *et al* used a standard photographic light meter to obtain their penetrance measurements (converted here to transmission values) which ranged from 0·3% for the commercially produced 'Bilimask' up to 48% for a single layer of stockinette material.[4] However, this data may be misleading as the instruments and the units of measurement chosen were inappropriate.[5] Photographic light meters are not specifically designed for performing transmission measurements and undoubtedly lack sufficient accuracy. In addition, when considering the potential hazards of phototherapy light to the cornea and/or retina, both the intensity and wavelength of light must be considered. Illuminance, as measured by Porat and associates, is a photometric unit and describes the intensity of light falling upon a surface weighted by the spectral sensitivity of the human observer (V_λ) as defined by the Commission Internationale d'Eclariage. The V_λ curve peaks in the yellow-green (555 nm) region of the visible spectrum whereas most phototherapy sources emit blue light (425–470 nm), and a small amount of ultraviolet radiation between 330 and 400 nm.

Chin *et al* measured the transmission of light through a variety of phototherapy eyeshields currently used in neonatal units in England.[3] These authors measured the transmission of light at wavelengths between 250 and 800 nm using a Perkin-Elmer 330 spectrophotometer (sensitivity 0·002%), a range which contained the spectral region in which energy from a phototherapy source is maximal. The commercial patches examined, which included the Bilimask manufactured by Olympic Medical, demonstrated a peak transmission of less than 0·02%, a figure matched or improved on by some of the home made eyeshields. But the optics of the system used permit the measurement of only directly transmitted light and thus this data may underestimate the total amount of light (direct and scattered) which penentrates the eyeshield.

Here we report a small study in which the transmission characteristics of eyepatches has been measured under conditions that attempt to mimic their use in a neonatal unit as closely as possible.

Materials and methods

A Macam SR300 spectral radiometer was used to perform the transmittance measurements. This consists of a Macam MCG201 monochromator, electrometer, silicon diode photodetector, liquid light guide 1000 mm long with a 5 mm active diameter and/or a sideview attachment with diameter 1·0 cm. The system has a bandwidth of 15 nm and has been calibrated in watts (W) (per steradian for radiance)/cm^2/nm correct at 510 nm against lights traceable to the National Bureau of Standards (NBS). Measurements at other wavelengths require the display reading to be modified by the multiplication factors given in the table. The Macam radiometer used has a calibrated spectral range of 380–740 nm and an uncalibrated range of 350–800 nm. Sensitivity for irradiance is 1×10^{-8} W/cm^2/nm.

Background light was nulled and the eyepatch placed over the detector head, the separation of detector and eyepatch being about 2 mm. A series of measurements of the irradiance (taken at 10 nm intervals between 400–700 nm) were then taken with the detector placed 35 cm from the phototherapy source (Vickers Medical 80/885). The eyepatch was removed from the detector head and the series of readings repeated to obtain baseline measurements. The percentage transmission at each wavelength was made by dividing each eyepatch reading by the corresponding baseline measurement and multiplying by 100.

Correction factors for each wavelength for the Macam SR300 spectral radiometer

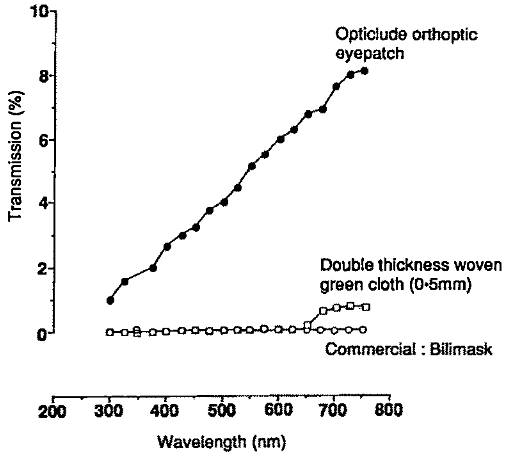
Wavelength (nm)	*Multiplication factor to obtain (W/cm²/nm)*
380	4·00
390	2·47
400	1·87
410	1·54
420	1·42
430	1·32
440	1·24
450	1·20
460	1·14
470	1·13
480	1·12
490	1·10
500	1·08
510	1·00
520	1·08
530	1·21
540	1·23
550	1·24
560	1·23
570	1·33
580	1·29
590	1·34
600	1·45
610	1·52
620	1·60
630	1·62
640	1·64
650	1·68
660	1·69
670	1·75
680	1·75
690	1·77
700	1·88

Three sets of measurements were made for each of three eyepatches: Olympic Medical Bilimask, Opticlude orthoptic eyepatch, and two layers of dual thickness woven green cloth, all three of which were similar to patches used in a previous study of transmission characteristics of eyepatches.[3]

Results and discussion

The figure shows the transmission measurements obtained for the three eyepatches. In the critical spectral region of 460 nm neither the Bilimask nor the green cloth had a peak transmission of greater than 4% at 700 nm and even for the poorest patch tested (Opticlude orthoptic eyepatch) this did not exceeed 10%.

Although our data may appear contrary to previously spectral transmittance characteristics of eyepatches used in England,[3] this is not entirely so: both the sets of data confirm that there is very little difference between the home made patches and commerically produced eyeshields. The difference in magnitude can be explained by variations in the apparatus used to perform the measurements. The Perkin-Elmer spectrophotometer used in the former study is correct for normal incidence transmission, while the data reported here includes the contribution of both normal and diffuse scattered light.



Light transmission characteristics of three phototherapy eyepatches.

It is possible to compare the two sets of data directly by considering the specifications of the detector system (see appendix) and differences in the systems explain the multiplication factor of ~100 between the two sets of measurements. Therefore although both sets of data are correct, the question remains—which set is most appropriate when considering the transmission characteristics of phototherapy eyeshields? We suggest that the data reported above are most appropriate for conditions under which eyepatches are used in clinical practice as they represent the amount of light reaching the eye or eyelid through the patch due to a combination of directly transmitted and scattered light. This does not invalidate the previous study, however,[3] or experimental methods employed, as the apparatus used permitted very accurate curves of light transmission to be plotted.

It is also pertinent to note that eyepatches are difficult to keep in place and may slip,[6] and indeed a recent report noted that they did not fully cover the eyes for 56% of observations.[7] This slippage may be explained by the difficulty in securing the eyepatches and perhaps the reluctance of the nursing staff to disturb an immature and hence tiny baby frequently for a task of perceived secondary importance compared with more immediate and life saving interventions. The choice of eyepatches should therefore take into account the simplicity and effectiveness with which they can be secured.

Appendix

After light has passed through the eyepatch one of two detector systems is present.

(1) It is assumed that light spreads from a point source of intensity I_o (W/cm²) as $I_o \cos\theta/l^2$ (the cosine rule) where θ is the angle from normal and L is the distance of the detector from the source. Thus any ring will gather:

$$I_g=(I_o \cos\theta. (\text{area}))/L^2$$
$$I_g=I_o \cos\theta\ (2\pi\ xdx)/L^2$$

$$I_g=\frac{I_o}{L}\int_{x=0}^{R}\frac{L}{(l^2+x^2)^{1/2}}2\pi xdx$$

$$=\frac{2\pi I_o}{L}\int_{x=0}^{x=R}\frac{x}{(x^2+L^2)^{1/2}}dx$$

For the Perkin-Elmer spectrophotometer: L~200 mm and R~7 mm hence

$$I_{gPE}=0{\cdot}385\times10^{-3}\ I_o$$

But, the phototherapy lamp must be considered as an extended rather than a point source so, for a radius of 4 mm

$$I_o \rightarrow I_o\ \pi\ (4)^2 \rightarrow I_{gPE} = 0{\cdot}019\ I_o$$

(2) For the Macam spectrophotometer: here the set up is for an extended source of which all the light incident on a given area is gathered.

$$I_{gM} = \frac{I_o\,\pi\,(5)^2}{2^2} \text{ for } r = 5 \text{ mm and } L = 2 \text{ mm}$$

$$= 19{\cdot}6\ I_o$$

Therefore the theoretical ratio between the measurements obtained by Chin *et al*[3] and those reported in this study should be:

$$\frac{I_{gM}}{I_{gPE}} = \frac{19{\cdot}6}{0{\cdot}019} = 103$$

These calculations also demonstrate that the intensity of the light falling on a surface declines with increasing distance from the source—the $1/R^2$ rule.

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CURRENT TOPIC

Anticonvulsants in pregnancy

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Epilepsy and pregnancy

Recurrent seizures affect at least 1% of women who are of childbearing age, but as the fertility of both men and women with epilepsy is slightly reduced,[1] about one in 200 pregnancies occurs in a woman with epilepsy. Most of these women are taking anticonvulsants regularly.

Pregnancy has an unpredictable affect on seizure frequency.[2 3] For half of the women with epilepsy there is no significant change in the frequency of convulsions when they become pregnant, but a quarter have more seizures than usual. That group includes many women who also tend to have more seizures when menstruating. An increase in the number of seizures during pregnancy is twice as likely if the fetus is male. (There are some women who only have seizures when carrying a male child and none when carrying a female.) Pregnancy itself is not particularly epileptogenic, however by chance epilepsy will sometimes present for the first time during pregnancy; such gestational epilepsy is more likely to be of a focal nature.[4]

Pregnancy affects the metabolism of anticonvulsant drugs in several ways. Those women who suffer severe hyperemesis early in pregnancy may fail to retain the usual dose of oral anticonvulsant, and thereby suffer an increase in seizures. Some drugs are less well absorbed during pregnancy, and for some there is a lower degree of protein binding.[5] Drug metabolism itself is altered. Pregnancy induces hydroxylating enzymes that lower the level of anticonvulsants such as phenytoin and phenobarbitone.[6 7] Fluid retention, and the extra tissues of the fetus and placenta that increase the volume of distribution of the anticonvulsant drug, may lower levels further.

The mother

The maternal mortality, from epilepsy, during pregnancy is low (approximately one fatality per year in England and Wales) but the number has remained steady in the last 50 years and, as other causes of maternal fatality have reduced, that occurring in women with epilepsy has become more prominent. As these fatalities occur as a result of accidents such as asphyxiation at the time of a generalised seizure, those treating pregnant women with epilepsy are likely to continue to seek the best possible control of the seizures with appropriate anticonvulsant therapy and to be wary of any drug reduction (even though it might benefit the fetus).

The pregnant woman with epilepsy is even more likely to become anaemic as a result of folic acid deficiency than someone who is not taking anticonvulsants; this is because most anticonvulsant drugs act as antagonists to folic acid. Although there is a slight worry that folate supplement may interfere with anticonvulsant metabolism,[8] for instance by lowering the serum phenytoin concentration, this is neither serious enough nor common enough to contradict the advice that a small folate supplement (in the range 100–1000 μg) be given each day to all women of childbearing age who take anticonvulsants regularly, and that it be continued throughout pregnancy.[9]

Vitamin D deficiency is a potential risk for women, and their fetuses, who are receiving long term phenytoin treatment. Phenytoin induces the production of enzymes that hydrolyse vitamin D, therefore, women receiving regular phenytoin should receive supplementary vitamin D throughout pregnancy.

The risk of complications of pregnancy in a woman with epilepsy is no greater than in a woman without epilepsy, though reports suggest that obstetric intervention, in the form of induction of labour and instrumental delivery, tends to be more prevalent when the mother has epilepsy (without there necessarily being good reason for such intervention).[10] The chance of spontaneous abortion or of multiple birth is not great, nor is there an increased risk of toxaemia.[11]

The infant

The incidence of babies who are either of low birth weight or who are preterm is similar for both epileptic and non-epileptic women. But the perinatal mortality rate is twice as high among babies of epileptic mothers who have been taking anticonvulsants regularly. This results partly from an increased incidence of spontaneous haemorrhage and partly from a higher incidence of severe congenital abnormality.[12]

Haemorrhage

Anticonvulsant drugs, particularly barbiturates or phenytoin, may depress the vitamin K dependent clotting factors, prothrombin and VII, IX, and X.[13] Such coagulation deficiencies led to reports of massive haemorrhages occurring in late pregnancy or shortly after birth: they tended to occur suddenly in unusual sites—intrathoracically or retroperitoneally.[14] Once it was realised that the coagulation defect was similar to that found in vitamin K deficiency it became possible to prevent and treat the coagulation abnormality.[15] Providing that the mother is given 10–20 mg of vitamin K during the last month of pregnancy, the occasional severe intrauterine fetal haemorrhage should be prevented, as should neonatal haemorrhage. In

ings to those from more than 20 large retrospective studies in showing that children of epileptic mothers have over twice as many major congenital malformations as children of mothers without epilepsy.[18] Therefore if a mother has epilepsy, and is taking anticonvulsant drugs,

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neuroblastoma occurring in children who have been exposed to phenytoin in utero.[22–24]

Of the more recent anticonvulsants, major concern surrounds sodium valproate. Ten years ago it was regarded as completely safe in pregnancy but there is now clear evidence of its association with neural tube defects.[25] The International Clearing House for Birth Defects monitoring systems suggest that the risk for a mother with epilepsy, taking sodium valproate during pregnancy, of having a child with spina bifida is approximately 1·2% compared with the risk of 0·06% for a woman who neither has epilepsy nor is receiving anticonvulsants.[26 27] As, with appropriate counselling and screening for neural tube defects in the first trimester of pregnancy, such abnormal babies may be aborted, there are those who feel that the therapeutic efficacy of sodium valproate for specific patterns of epilepsy, such as juvenile myoclonic seizures, justifies its continued use in women of childbearing age providing that the risks and the options are discussed with the mothers. There are also reports that the offspring of such mothers have long term neurodevelopmental problems. This is a particularly difficult area to evaluate because of the different genetic, social, and environmental factors that contribute to a child's development. It is a sad fact that many children whose parents have severe epilepsy live in a disadvantaged environment.

For many years carbamazepine was considered extremely safe but the report from California last year of children identified both retrospectively and prospectively after exposure to carbamazepine in utero yielded the familiar pattern of minor craniofacial defects, fingernail hypoplasia, and neurodevelopmental delay that has been reported so often in the past with other anticonvulsant drugs.[28] Benzodiazepines are less likely to be used as mainstay therapeutic treatment for epilepsy but, when they are taken regularly throughout pregnancy, they too probably increase the chance of a baby with dysmorphic features and developmental delay.[29]

Several studies suggest that abnormalities are more likely if more than one anticonvulsant is used or if particularly large doses are taken.[18]

The teratogenic effect

The many large surveys revealing the increased incidence of congenital abnormalities in the infants of mothers who took anticonvulsants could not include a similar number of mothers with epilepsy who were *not* receiving anticonvulsants. Thus there has always been difficulty in establishing, with certainty, that it is the anticonvulsant drugs that are associated with fetal abnormality rather than epilepsy. Fifteen retrospective comparative studies did not find an increase in the incidence of congenital malformation in epileptic mothers who did not receive anticonvulsant drugs compared with the general population.[18] However, it can be presumed that woman with epilepsy, who are not taking anticonvulsant drugs, have much less severe epilepsy than those receiving anticonvulsant drugs, and therefore there remains the possibility that severe epilepsy itself is associated with congenital abnormality.

People with epilepsy are more prone to certain congenital abnormalities: cleft lip and palate and congenital heart disease, which itself is preferentially associated with clefts.[30 31] However, that association is not strong and cannot account for the more than twofold increase in congenital abnormalities in babies born to mothers with epilepsy.

Moreover, two studies have shown that the children of men with epilepsy do not have an increased rate of severe congenital malformation, or of facial clefts, compared with the children of men in the general population.[32 33] Few will dispute that women with severe epilepsy have a limited choice of husband and, therefore, that their child may be less fortunate in its genetic endowment. Nevertheless, the conclusion is that there are very strong grounds for believing anticonvulsant drugs to be teratogenic. That conclusion is supported by several surveys which have failed to find any link between the severity of epilepsy, the type of epilepsy, or the frequency of seizures during pregnancy and congenital abnormalities in the child. Seizures, per se, do not seem to lead to congenital abnormality.[2]

The teratogenic effect is most likely to occur from 18–56 days after fertilisation, after that, although functional abnormality may occur, structural abnormality is unlikely. It may be relevant that some anticonvulsants have a higher concentration in the fetal bloodstream than in the mother's. The fetus is exposed to a much higher valproic acid concentration than the mother as a result of decreased maternal serum protein binding and raised maternal free fatty acid concentrations.[34] Diazepam is also raised preferentially,[35] and, as the mother tends to have raised free fatty acid concentrations early in pregnancy, the fetus is particularly likely to be exposed to high concentrations of sodium valproate and diazepam at that time.

The mode of the teratogenic effect is unknown. It has been popular to suggest interference with folate metabolism, as most anticonvulsants lower serum folate and there is much work showing that folic acid antagonists do, and folic acid deficiency probably does, induce congenital defects.[36] Nevertheless it may be that particular products of anticonvulsants are themselves toxic. The link with the role of poor nutrition in the aetiology of congenital abnormalities may be relevant, particularly as people who are short of folate are often short of other vitamins and essential nutrients. (The author will never forget the mother of the index case in the figure who came from a most disadvantageous background, and in addition to frequent generalised seizures had the most severe hyperemesis, pronounced anaemia, and undernutrition.) Thus it is understandable that doctors who advise a compound vitamin for women of childbearing age who are planning to have children, will do so even more readily for a woman who has epilepsy and is receiving anticonvulsants.

The puerperium

Anticonvulsants cross the placenta freely. The rate of clearance in the neonate varies according to the drug and is believed to be in the range of 8–28 hours for carbamezapine, 14–88 hours for sodium valproate, 15–105 hours for phenytoin, and 40–500 hours for phenobarbitone.[37] [38] Such newborn infants may suffer harmful effects from that anticonvulsant level and, as a group, tend to be less efficient at feeding and to gain weight more slowly. A minority will suffer withdrawal symptoms such as tremor, excitability, and seizures (best treated with phenobarbitone). Anticonvulsants pass into the breast milk in relatively small quantities. The ratio between breast milk and serum concentrations is reported to be less than 0·1 for sodium valproate,[38] 0·19 for phenytoin, 0·36 for phenobarbitone, and 0·41 for carbamezapine.[39] Neither maternal epilepsy nor maternal treatment with anticonvulsant drugs are contraindications to breast feeding.

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PERSONAL PRACTICE

Resuscitation of the newborn

A D Milner

Despite even the most diligent care and monitoring, problems sometimes arise during labour that cause fetal asphyxia and lead either to death or to brain damage. As paediatricians, however, we cannot accept circumstances in which asphyxial damage occurs after delivery as a result of inadequate facilities, staffing levels, or training.

Since intubation and positive pressure ventilation were first recommended by Flagg in North America in 1928,[1] and by Blaikley and Gibberd at Guy's Hospital in 1935,[2] a pattern of resuscitation had evolved based on extrapolation and assumption rather than on clinical measurement. There can be few areas of medicine in which the potential benefit is so great but which have been subjected to so little evaluation.

Physiological measurements of lung expansion at birth

In the absence of well controlled clinical trials, one logical approach is to assess how a healthy

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trunk was still in the birth canal.[5] The volume changes were similar, with a mean inspiratory volume of 40·3 ml and a mean functional residual capacity of 18·7 ml. The inspiratory pressures were a little higher (mean 33 cm H_2O, range 6–103) but again an opening pressure was rarely seen, with air entering the lungs as soon as the intrathoracic pressure began to fall. In retrospect this is not surprising as the air/water interface immediately before the first breath is in the oropharynx rather than at the terminal bronchiolus.

The opening pressure phenomena described by Karlberg *et al* and seen in some of the Nottingham babies occurred because the water filled respiratory system has a relatively slow response time, compared with diaphragmatic contraction. This phase effect will be exaggerated in babies who are relatively asphyxiated and start to breathe with inspiratory gasping.

A further problem with all these studies is that pressures will be under-recorded if the (range 0·20–1·4), and significant correlation was noted between the product of the inspiratory pressure and time, and the formation of a functional residual capacity.[6]

Physiological measurements during resuscitation

INTUBATION

These studies indicate that the resuscitation techniques currently recommended are significantly different from the pressure sequences found in the spontaneously breathing baby and may be less effective. This is borne out by what information we have on the efficacy of routine resuscitation at birth. Boon *et al* measured the volume changes associated with the use of an inflation pressure of 30 cm H_2O maintained for about one second in full term babies requiring resuscitation at birth.[8] They found that this produced a mean volume change of only 15·3 ml (range 0–62·5) and in only three of the 20 was there a measurable volume of air in the lungs at the end of the first inflation, compared with 48 of 50 babies who started breathing spontaneously.[9] In many babies the tidal exchange produced was actually less than the anatomical dead space and so was not producing effective ventilation. Analysis of the babies' response to the first few inflations showed that the most common response was for the baby to produce a high positive intrathoracic pressure[10]; this obviously impeded lung expansion. At other times the inflation pressure stimulated the baby to make inspiratory effort—the so called 'Heads' paradoxical reflex. This often led to remarkable improvement in the mechanical characteristics of the lung and the formation of an appreciable functional residual capacity. Inspection of the tidal volume trace showed that at the end of one second air was still entering the lungs—that is, the respiratory system was responding slowly to the inspiratory pressure. When this first inflation pressure was maintained for more than three seconds the mean inspiratory volume rose to 33·5 ml (range 16·9–70) and the mean functional residual capacity to 15·9 ml (range 11·7–31·0), that is, figures similar to those achieved by babies who were breathing spontaneously.[11] This prolonged inflation may also have compensated for the inevitable loss of the first cry.

In all these studies the inflation pressure was kept constant, so no allowance was made for differences in lung mechanics among babies. Further information on the most appropriate pressure was provided by Hull who used a volume limited system and attempted to inflate the lungs of babies who required resuscitation with a constant volume; he then measured both the resulting pressure and the rate at which a functional residual capacity was produced.[12] He found that although there were some who could be resuscitated satisfactorily with pressures of less than 30 cm H_2O, others required pressures in excess of 40 cm H_2O.

The generally recommended upper limit of 30 cm H_2O has been justified on the grounds that pressures in excess of this would be more likely to produce a pneumothorax. Our only information on this derives from a paper by Rosen and Laurence who subjected the isolated newborn lung to the increasing pressures until rupture occurred.[13] This was a common occurrence once 60 cm H_2O had been exceeded, but rarely occurred when the pressure was below 35 cm H_2O. This is, however, an artificial situation and analagous to identifying the maximum possible pressure for a car tyre by blowing up the isolated inner tube until it ruptures.

In many units throughout the world babies are resuscitated with anaesthetic rebreathing bags attached to the endotracheal tube by the criteria recommended by anaesthetists—that is, generating sufficient pressure to produce visible movement of the chest wall. This technique was used in a recent study on the resuscitation of 29 babies, and at the same time both the tidal exchange and inflation pressure were measured.[14] The mean inflation pressure was then 49·1 cm H_2O (range 35–67 cm H_2O) falling to 39 cm H_2O (range 28–57 cm H_2O) at the end of the period of resuscitation. Interestingly, in the full term babies this produced tidal volumes of 40 ml and often led to the formation of a functional residual capacity despite inspiratory times in the region of only half a second. As will be noticed, these figures are virtually identical to those achieved by babies who started breathing spontaneously.

FACE MASK RESUSCITATION

Bag and mask systems have been available for use in the labour ward for many years. These usually incorporate blow off valves, which are relatively crude in function and heavily dependent on the flow. Measurements made with five devices currently available showed that those with bag volumes of less than 300 ml rarely produced ventilation greater than the anatomical dead space.[15] When the bag was at least 500 ml in volume, inflation volumes were closer to those achieved with conventional resuscitation. The main reason for this was that the larger bag allowed the inflation pressure to be maintained for longer. Even with these, however, it is likely that the apparent success achieved with these devices in the labour suite results largely from the induction of a Heads paradoxical reflex, rather than by achieving adequate ventilation alone. An alternative approach has been to attach a T piece to a soft, ring shaped face mask, to incorporate a blow off system in the inspiratory line, and to occlude the T piece intermittently with a finger.[16] This is a much easier device to use, it can be applied with one hand leaving the other one free either to steady the head or to hold the stethoscope bell to the chest, and it produces appreciably better tidal exchange as it allows inflation pressure to be maintained for at least a second. Current experience in Nottingham indicates that the routine use of this device can reduce the need for intubation by up to half. Although this was considered to be an innovation, the device was first described in the *American Journal of Medicine* in 1926 and then seemed to have disappeared from use for nearly 60 years.[17]

As stated earlier, though these measurements give us information on the relative efficacy of the different methods and patterns of resuscitation, what is totally lacking is any controlled trial comparing long term outcomes. Such a study would be extremely difficult to carry out, and would have to be large; failing this it seems reasonable to use the information available when drawing up a resuscitation protocol.

MANAGEMENT AT BIRTH AND INDICATION FOR RESUSCITATION

Although the Apgar score may be of some epidemiological interest it is of little help in determining which babies will require resuscitation, and of limited value in determining either short term or long term outcome.[18] It is obviously essential to reduce heat loss by wiping excess water off the baby during the first few seconds, ensuring that the baby is in a relatively warm environment, and that there are no gross congenital abnormalities that might deter one from proceeding to resuscitation. Providing that the baby's heart rate is in excess of 80/minute, it is acceptable to delay intervention for up to a minute even if there are no respiratory efforts whatsoever. Nasopharyngeal and oropharyngeal suction are sometimes carried out on the assumption that this will stimulate the baby to breathe. There is, however, good evidence that overenthusiastic pharyngeal suction can actually delay the onset of respiration, and this manoeuvre is probably not indicated unless the upper airway is contaminated with blood or meconium. It remains entirely acceptable to stimulate the baby gently—for example, by flicking a foot. If by 1 minute of age the baby is still making inadequate respiratory efforts, mask and T piece resuscitation should be started, and an inspiratory pressure of 20 to 30 cm H_2O should be maintained for at least a second initially.[16] If this device is not available, a bag and mask system will often be successful, particularly if the inflation bag has a volume of at least 500 ml.

If this form of resuscitation fails to achieve adequate air entry, or if the baby's heart rate falls to less than 80/minute at any time after delivery, intubation will be required, Again, maintaining the first inflation for two to three seconds will lead to a more rapid resolution of hypoxia. Start with inflation pressures of 20 to 30 cm H_2O, but it may be necessary to raise this to 40 or even 50 if air entry is poor—particularly if there has been oligohydramnios or the infant has a diaphragmatic hernia that has been diagnosed antenatally—both conditions that are associated with pulmonary hypoplasia.[19]

There seems little reason not to use 100% oxygen in the resuscitation of full term babies. There was a theoretical worry that absorption atelectasis might occur more often if this was done, particularly if the baby tended to hypoventilate after extubation. There is no evidence to show that this does occur, however, and indeed breathing 100% oxygen for up to 15 minutes in the first hours of birth has no measurable effect on lung volume,[20] probably because microbubbles are formed, which persist in the lung until lung fluid absorption has occurred.[21]

EXTERNAL CARDIAC MASSAGE

If peripheral pulses are absent and the apex beat is either imperceptible or less than 60/minute, external cardiac massage should be started. There is now little doubt that the 'hands round the chest method'—that is placing the tips of the fingers along the spine and compressing the lower sternum with both thumbs, produces better cardiac output than compressing the sternum with the index and middle fingers alone.[22] The aim should be to produce three chest compressions for every lung inflation. Sometimes this is sufficient to lead to an obvious improvement. For the remainder it will be necessary to start treatment with drugs.

DRUGS IN RESUSCITATION

By this stage the babies have inevitably developed severe metabolic acidosis, almost certainly with a pH of less than 6·8. Although adrenaline is more likely to work after this acidosis has been at least partly relieved, if it is given directly down the endotracheal tube (0·5 ml 1/10 000), it does sometimes have an immediate effect.[23] It is reasonable to try this while arrangements are made to give 4·2% sodium bicarbonate (20 ml to a large baby) either through an umbilical venous catheter or by direct injection into the vein within the cord. Once this has been given, further doses of adrenaline can be given either directly into the umbilical vein or again down the endotracheal tube. This response to endotracheal adrenaline is surprising in view of the fact that the pulmonary circulation is extremely small before the onset of spontaneous ventilation. Babies who fail to respond to adrenaline and external cardiac massage are sometimes given calcium gluconate, although evidence that this is useful is lacking.

When resuscitation has led to good chest wall movement, symmetrical air entry, and improvements in cardiac output and appearance but respiration fails to start, respiratory depression from opiates given to the mother should be considered. It is then appropriate to give intravenous naloxone 20–40 μg. If this produces a response it is recommended that an additional 200 μg should be given intramuscularly to produce a more prolonged effect.

WHEN TO STOP

There have now been a number of studies that showed that babies who take up to 20 minutes to respond, even after the most intensive resuscitation, can subsequently develop entirely normally.[24–26] Such an outcome is rarely seen, however, in babies who have failed to produce even intermittent respiratory efforts by 30 minutes. For this reason many units have now adopted a policy of withdrawing treatment at 20 to 30 minutes from those who fail to show any sign of life other than an effective cardiac output, but if necessary they provide supportive ventilation for the next 24 to 48 hours. A proportion of these babies will inevitably die from severe asphyxial encephalopathy. There is currently some dispute about the number of these babies who will subsequently be entirely normal, and estimates range from 30 to 85%.[27]

RESUSCITATION OF PRETERM BABIES

Most babies of over 32 to 34 weeks' gestation will start to breathe spontaneously without any problems. The more immature the baby, the more likely it is that intervention will be required. Some units will electively intubate and ventilate all babies of less than 28 or even 30 weeks' gestation at birth on the grounds that this will ensure that the baby's lungs are expanded rapidly and reduce the incidence of subsequent respiratory distress. This policy is often adopted if the distance between the labour suite and the neonatal unit is substantial and there are worries that the baby may deteriorate during transport. There is one published study that shows that when a policy of elective intubation is compared with rigid intubation criteria—that is, only 3% of babies of less than 30 weeks' gestation—elective resuscitation was associated with a reduction in mortality from 70 to 50%.[28] A further smaller study (DJ Field, AD Milner, unpublished observations), in which an intermediate policy was adopted—that is babies not breathing regularly by 30 seconds were given bag and mask resuscitation, and those not breathing regularly by 1 minute were intubated—produced results that were identical to elective intubation for all babies. This is the policy that we have adopted in Nottingham, where we intubate between 60 and 70% of all babies of less than 30 weeks' gestation.

There are some centres that regularly use 40% oxygen for resuscitating preterm babies on the grounds that high oxygen exposure even for a short time might increase the incidence of retrolental fibroplasia. It is, however, extremely unlikely that exposure to 100% oxygen for even 15 to 20 minutes is likely to have any long term adverse effects. There has also been some dispute about the inflation pressures that should be used for preterm babies. It is recognised that preterm babies are more prone both to pneumothoraces and to pulmonary interstitial emphysema. These are less likely to occur if low inflation pressures are used. Preterm babies are likely to be deficient in surfactant, however, and so may need relatively high inflation pressures to achieve adequate tidal exchange and form a functional residual capacity. What information is available suggests that endotracheal resuscitation of preterm babies with 30 cm H_2O pressure is less likely to produce adequate alveolar ventilation than in full term asphyxiated babies.[29] On the other hand, the study in which babies were ventilated with an anaesthetic rebreathing bag showed no tendency for higher pressures to be required as gestational age fell, but there was a significant relationship between failure to form a functional residual capacity and the development of respiratory distress syndrome and subsequent death.[14] On balance, it seems reasonable to start with a pressure of 20 to 25 cm H_2O but to raise this if resuscitation fails to produce chest wall movement and satisfactory breath sounds.

There remains the problem of babies whose gestational age is less than 26 weeks. In some units the policy is to intubate babies even if the gestational age is as young as 23 or 22 weeks, and then proceed if necessary with supportive ventilation until the outcome is obvious. Other units practise more measured responses, only proceeding to intubation in those babies who make some respiratory efforts and are obviously of at least 23 to 24 weeks' gestation. I am more in sympathy with the latter than the former. Further studies are obviously needed to resolve this difficult ethical dilemma.

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CURRENT PROBLEM

Pathophysiology of apnoea in preterm infants

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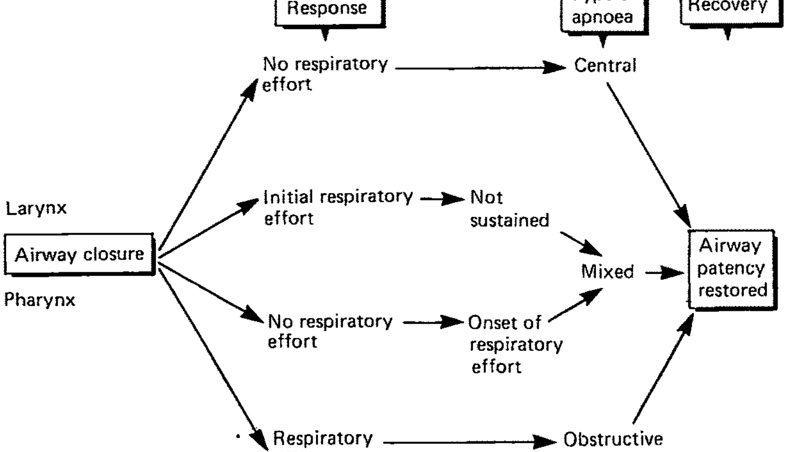
Apnoea is usually divided into three main types: central, obstructive, and mixed, the last of which contains elements of the first two. Recent investigations, however, have suggested that this division is less clear cut, and may be both artificial and misleading in terms of aetiology and therapeutic approaches. This division may be more a reflection of the inadequacies of the monitoring equipment that is used to detect apnoea in infants than of any real difference in the underlying pathophysiological processes.

The upper airway

INCREASING EVIDENCE FOR AN IMPORTANT ROLE

Although pure obstructive apnoea (defined as continued respiratory efforts with no flow of air) is relatively uncommon—about 12% among preterm babies—if those infants with mixed apnoea are included then about 70% of preterm infants with apnoea have episodes of airway obstruction.[1] Recent work has shown that airways are closed during the 'central' part of mixed apnoea during which respiratory efforts are absent as well as during apparently 'pure' central apnoea. When flow is detected by a face mask system that incorporates a pneumotachograph and sensitive pressure transducer, a cardiac artefact can be detected on the recorded flow trace. When the upper airway closes this artefact disappears, so it can therefore be used as an indirect indicator of the patency of the airway. Using this method closed airways have been detected in about half the cases of apparently 'central' apnoea (unpublished observations). It is therefore clear that closure of the airway is common to all forms of apnoea, and possibly has a central role in the pathophysiology of apnoea. The figure shows diagramatically how airway closure, and the infant's response to it, may give rise to the apparently different types of apnoea.



Obstruction of airways giving rise to apparently different types of apnoea.

SITE OF OBSTRUCTION

The two most likely sites of loss of upper airway patency on anatomical and physiological grounds are the larynx and pharynx.

Larynx

The larynx of a newborn infant has been described as 'a grossly enclosing composite of skeleton and musculature and a more discretely mobile, internal composite'.[2] The laryngeal vestibule of the infant is small in all diameters, particularly in relation to the lumen of the trachea, making it anatomically a likely site for obstruction.

It is often difficult to intubate apnoeic infants, because instead of finding the cords widely open as one might expect in a hypoxic, 'flat' baby they are often quite tightly adducted on laryngoscopy. Resumption of respiratory efforts against such a closed glottis has also been described. This may indicate that the larynx is the site of upper airway obstruction in apnoeic preterm infants.[3] Using an ultrafine fibreoptic endoscope passed transnasally we have seen obstruction at the laryngeal level in some preterm infants with problematical apnoea. The obstructing structures seem to be disproportionately large arytenoid masses and aryepiglottic folds. We have seen such obstruction not only in obstructive apnoea but also in the central part of mixed apnoea and in apparently pure central apnoea, which correlates with the findings of indirect indicators of airway patency (unpublished observations).

'Laryngeal chemoreflex' in preterm infants is well known[4]; this can be stimulated with boluses of fluid of as little as 0·01–0·1 ml instilled into the oropharynx. The response seems to be chemosensitive, there being a greater response to water than saline rather than simply a mechanoreceptor reaction in response to the presence of the bolus.[5] Stimulation of this reflex produces swallowing, airway obstruction, and apnoea that may at times be prolonged. This reflex is thought to protect the airway, and many features of it are similar to spontaneous apnoea seen in preterm infants.[6] It has been suggested that apnoea represents an exaggeration of this protective reflex in preterm infants.

Infants with malformations of the central nervous system such as meningomyelocele, Arnold-Chiari deformity, and hydrocephalus, which result in paralysis of the abductor cord secondary to raised intracranial pressure, commonly get apnoea and upper airway obstruction.[7] Direct electrical stimulation of the superior laryngeal nerve also produces glottic closure that is followed by prolonged apnoea in monkeys. This is a reflection of the degree of maturation, with preterm and newborn monkeys having more extreme apnoea after stimulation than older monkeys.[8]

Pharynx

The pharynx is a muscular tube without any rigid support. When subject to negative intraluminal pressure (as during inspiration) the tendency is for the walls of the pharynx to collapse. The upper airway muscles, such as the genioglossus and geniohyoid, are important in counteracting this tendency and in maintaining pharyngeal patency.[9] Reduced tone in these muscles, as one might expect in preterm infants or during rapid eye movement sleep, may predispose to upper airway obstruction. The oropharynx has been identified by radiography, electromyography, and laryngoscopy as the site of airway obstruction in adults and older infants with obstructive sleep apnoea.[10 11]

A catheter filled with saline and placed in the pharynx has been used to monitor pharyngeal pressure changes in preterm infants with apnoea.[12] Results have suggested that airway obstruction occurs high in the oropharynx and above the catheter tip in over 90% of episodes. The position of the catheter tip in these studies is critical and it was judged only by the pressure changes seen in normal breathing and swallowing and not confirmed laryngoscopically or radiologically. There is, however, good evidence of the importance of the function of muscles of the upper airway such as the genioglossus in the recovery of apnoea,[13] as increased electromyographic activity is recorded at the end of an episode, which leads to restoration of airway patency.[14] Infants with mixed and obstructive apnoea may respond to occlusion by reducing the activity of these muscles.[15]

There is therefore evidence to suggest that in apnoeic episodes airway patency may be lost at either laryngeal or pharyngeal level. It is also possible that obstruction at one of these sites may, by causing cessation of airflow, produce the collapse of the other.

Central immaturity

Immaturity in the control of respiratory activity clearly plays an important part in the pathophysiology of apnoea of prematurity. There is now accumulating evidence of adaptation of higher centres—including those of respiratory control—that are gestation dependent. The ventilatory response to carbon dioxide shows a striking difference in preterm infants with apnoea when compared with controls. Infants with apnoea have depressed ventilatory responses to hypercapnia and other measures, suggesting that there is a reduced respiratory centre output that is independent of overall pulmonary function.[16] When the effect of increasing anatomical dead space was examined by analysing the response to tube breathing, however, it was found that although most immature infants had poor respiratory adaptation, there was no deficit in control in babies with apnoea once correction for postconceptional age had been made (unpublished observation).

Further evidence of brain stem immaturity comes from measures of neuronal function in preterm infants with apnoea. Auditory evoked responses have been used to measure brain stem conduction times, which were significantly increased in babies with apnoea compared with controls matched for gestational age.[17] Apnoea also resolved once the brain stem conduction times fell to the same level as babies without apnoea. Similarly, when the glabellar tap response and its augmentation by auditory stimuli was investigated, a group of infants with problematical apnoea showed significantly reduced augmentation, which implied immaturity of brain stem neuronal function and organisation.[18]

Assessment of peripheral chemoreceptor reflexes showed that they have little part to play in the onset of apnoea in preterm infants. There is evidence they are active by 28 weeks' gestation, and responses to high and low inhaled oxygen concentrations do not seem to change significantly with increasing gestational age.[19]

Periodic breathing—a respiratory pattern consisting of recurring cycles of breaths and respiratory pauses—is a common finding in preterm infants who spend up to 40% of the time breathing in this way.[20] It decreases with gestational age, being less common in more mature babies, and is therefore another marker of immaturity of respiratory control, although it is generally agreed to be of no pathological importance. It seems that periodic breathing is not a precursor of apnoea,[21] although it decreases in frequency with advancing gestational age and responds to treatment with one of the xanthine group of drugs. Upper airway obstruction is also common in periodic breathing.[22] Similar pathophysiological processes therefore seem to be operating in periodic breathing as in apnoea of prematurity, although the occurrence of one does not necessarily lead to the other.

There are also differences in respiratory reflexes in preterm infants and in those experiencing apnoea. In response to increased respiratory loads infants with apnoea maintain inspiratory efforts poorly with shorter inspiratory times.[23] Airflow obstruction can cause apnoea in preterm infants,[24] either spontaneously when the neck is in certain positions[25] or experimentally by occlusion with a mask.[26] We should be cautious about extrapolating from the response to an experimentally induced occlusion compared with naturally occurring obstruction during apnoea, however, as there may be differences in the responses of the respiratory muscles.[14]

The chest wall becomes more stable with increasing gestational age and dynamic measurements of diaphragmatic function are achieved. The improved stability seems to parallel the resolution of apnoea of prematurity and it may be that reduced diaphragmatic work may contribute to this.[27] Preterm infants also show

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matter for some debate. Its effect on the lung function of infants is to reduce minute ventilatreatment (by—for example, reserving theophylline for central apnoea and CPAP for obstructive apnoea) but should be prepared to try different treatments alone or in combination. We hope that as more details of the important pathophysiological factors are brought to light, new therapeutic options will be suggested.

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REGULAR REVIEW

Treatment of persistent pulmonary hypertension of the newborn: update

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Persistent pulmonary hypertension of the newborn is primarily characterised by persistence of, or return to, the suprasystemic pulmonary vascular resistance and pressure normally found in the fetus. The increased pulmonary pressure causes right to left shunting through the ductus arteriosus or the foramen ovale, or both. The resulting hypoxaemia and acidosis may produce further pulmonary vasoconstriction and lead to a vicious cycle of shunting, hypoxia, and acidosis.

Aetiology

About half the pulmonary arteries in a newborn infant contain muscle. Abnormal formation of muscle in the small pulmonary arteries can occur before or after birth and is characteristic of all forms of pulmonary hypertension in childhood. Smooth muscle precursors (the pericytes and the intermediate cells) can develop into mature smooth muscle cells within days if 'switched on' by an effector—for example, hypoxia, increased pulmonary pressure or blood flow, mediators, or endothelial cell damage.[1] [2] These changes in turn reduce the total pulmonary cross sectional area either directly or by enhancing thrombosis.[3] Persistent pulmonary hypertension of the newborn was initially described in asphyxiated infants who were cyanosed with relatively normal lungs, and right to left shunting in infants without congenital cyanotic heart disease. Infants with persistent pulmonary hypertension of the newborn are usually full term or post term infants, and often have had perinatal asphyxia (13%), meconium aspiration (66%), or diaphragmatic hernia, pneumonia, or sepsis (21%).[4–7]

Incidence

Accurate estimates of the incidence of persistent pulmonary hypertension of the newborn are not available, but estimates of about 1/1500 live births with a range from 1/1454 to 60/2602 have been reported, which accounts for about 1% of admissions to neonatal intensive care units.[7] [8]

Risk factors for death

The average mortality is about 40% (range 34%–60%) despite aggressive management with hyperventilation, fluids, vasopressors, and vasodilators.[4–7] Infants with alveolar–arterial oxygen gradients (A–aDO_2) of 82·46 kPa all die, and among those with A-aDO_2 of 79·8 kPa or more for 12 hours the mortality was 94%.[5]

Clinical presentation

Persistent pulmonary hypertension of the newborn may present with severe hypoxia, severe acidosis, tachypnoea, tricuspid or mitral regurgitation, patent ductus arteriosus, hypovascularity on the chest radiograph, relatively clear lung fields and no anatomical cardiac lesions. The patient may develop right ventricular heave, electrocardiographic changes of myocardial ischaemia, and right ventricular overload. The disease may present immediately after birth—for example, in asphyxiated infants or those with diaphragmatic hernia with severe lung hypoplasia. It may present after 4–12 hours (subacute)—for example, in infants with meconium aspiration syndrome, or it may present after 12–24 hours (late)—for example, infants with sepsis and those with progressive airways obstruction.[4–7] [9]

Treatment

The aetiological diversity of the disease means that no single treatment will be uniformly effective. No controlled comparisons of treatments have been carried out. Once it has been diagnosed, therapeutic efforts should be simultaneously directed towards the specific treatment of the particular cause suspected and towards the reduction of pulmonary vascular resistance. All infants should be given a broad spectrum antibiotic. Adequate blood pressure should be maintained with vasoconstricting drugs and fluid infusions. Alkalis should be given to achieve a normal arterial pH if there is metabolic acidosis. Mechanical hyperventilation has been used to decrease pulmonary pressure and achieve normal oxygenation.[4] A very low carbon dioxide tension has a potentially deleterious effect on cerebral and renal blood flow. Complications include chronic lung disease (31%) and pneumothorax (45%).[9] Muscle relaxants and sedatives are used to prevent agitation and fluctuations in oxygen tension. Extracorporeal membrane oxygenation has been used to treat persistent pulmonary hypertension of the newborn with varying degrees of success, and survival has been reported as ranging from 58 to 100%.[5] [10] Several serious complications have been reported, however, and this type of treatment is not available at most neonatal centres. A conservative approach has sometimes been used,[11] but I know of no controlled trials that test the efficacy of this treatment.

Pulmonary circulation vasodilators

There are no drugs that specifically dilate the pulmonary vasculature and reduce pulmonary hypertension. Consequently our experience has been limited to trials of vasodilators that have been developed to control systemic hypertension with variable success.

ARACHIDONIC ACID AND ITS METABOLITES

Archidonic acid metabolites play an important part in the normal regulation of pulmonary vascular tone and in the pulmonary vascular responses to various pathological stimuli.[12] There are two pathways of arachidonic acid metabolism, which synthesise most of the biologically important eicosanoids: the cyclo-oxygenase pathway

[redacted]

different biochemical agents.[20] Prostaglandin E_1,[12] PGI_2,[21] and prostaglandin D_2[22] have been used to try and reduce pulmonary hypertension, but with inconsistent results and many complications.

VASCONSTRICTIVE EFFECT OF CALCIUM

Contraction of the smooth muscle cells in the walls of blood vessels and the consequent reduction of tissue perfusion is initiated when the cytoplasmic free calcium concentration rises above 0·1 mmol/l.[16 23] This increase could be the result of mobilisation of calcium from intracellular calcium pools or to increased permeability of the cell membrane to extracellular calcium because of the increase in endogenous vasoconstrictors, together with hypoxia or ischaemia.[16 23-24]

CALCIUM CHANNEL BLOCKERS

Pulmonary vasoconstriction is dependent on the availability of calcium to the affected cells,[25] and so calcium channel blockers have been given in an attempt to induce pulmonary vasoenzymes and is a necessary cofactor for ATPase. Thus magnesium is a vital cofactor in the maintenance of several energy demanding processes at the cellular level such as oxidative phosphorylation, neuromuscular excitability, and muscle contraction.

Lipman *et al* have shown that a continuous intravenous infusion of magnesium sulphate can control sympathetic crises and suppress the release of catecholamines.[37] Magnesium sulphate also activates adenyl cyclase, which plays a part in the synthesis of cyclic AMP.[38] increases in the amounts of cyclic AMP in smooth muscle promote relaxation by inhibiting the activity of myosin light chain kinase caused by accumulation of calcium by the sarcoplasmic reticulum, and resulting in a fall in intracellular free calcium to concentrations at which the myosin light chain kinase is not active.[39] The effect of magnesium on cyclic AMP is of particular interest because there are data that suggest that increased cyclic AMP concentrations promote vasodilation.[40] Magnesium sulphate causes peripheral arteries to dilate by various mechanisms. An indirect curare like action retards the release of acetylcholine and interferes with transmission at the neuromuscular junction and sympathetic ganglia. A direct action of the cation reduces the responsiveness of smooth muscle to sympathomimetic amines as well as to non-sympathomimetic vasopressors.[37 41–42] After an episode of ischaemic anoxia, concentrations of arachidonic acid rise rapidly in anoxic neurons.[43] The influx of calcium ions to anoxic arterioles results in vascular spasm.[44] In animal studies, magnesium antagonises calcium ion entry thereby promoting vasodilatation and alleviating the effect of severe hypoxia on the brain, liver, and kidneys.[45–48]

Thrombosis and consumption of platelets occur in small blood vessels in pulmonary hypertension.[3 19] Magnesium has an antithrombotic effect which—at least theoretically—has a role in the treatment of pulmonary hypertension.[49]

In patients with severe hypertension of pregnancy, Cotton *et al* found that both systemic vascular resistance and pulmonary vascular resistance fell after magnesium sulphate was given, and by 30 minutes had returned to baseline values.[50] McMurtry *et al* showed in isolated rat lungs that calcium antagonists inhibited hypoxic pulmonary vasoconstriction and that the hypoxic mechanism was critically dependent on the transmembrane influx of extracellular calcium.[51] Similarly, inhibiting hypoxic vasoconstriction in dogs by increased plasma concentrations of magnesium chloride[52] was possibly related to calcium antagonism by magnesium.[46–47] Cropp showed in dogs that there was a pronounced rise in pulmonary vascular resistance during hypoxia with normal concentrations of magnesium in the blood. As the magnesium concentrations were increased, the rise in pulmonary vascular resistance during hypoxia decreased. Hypoxic pulmonary vasoconstriction usually did not occur if magnesium rose above 5 mmol/l. Magnesium concentrations of less than 6·5 mmol/l did not cause hypotension or hypoventilation. He concluded that a controlled increase in the blood magnesium concentration to 5–6 mmol/l will block hypoxic pulmonary vasoconstriction without causing deleterious changes in haemodynamics or pulmonary ventilation. Attempts to use magnesium to decrease the pulmonary hypertension that was induced by hypoxia were not investigated in these studies.[52]

Paidas *et al* showed that continuous infusion of ATP and magnesium chloride produced a significant decrease in mean pulmonary artery pressure after induced hypoxia with little or no systemic side effects. They also reported that magnesium chloride had no effect when infused alone.[53] The doses of magnesium chloride given were small and the concentrations in serum were not measured. It is well known that a slight or moderate rise in blood magnesium does not affect the circulation. This study did, however, show the effect that magnesium preparations had in reducing pulmonary arterial pressure and resistance, and their likely useful therapeutic effect in pulmonary hypertension syndromes, but it failed to show the effect of magnesium alone because of the study design. Oral treatment with magnesium aspartate hydrochloride has been shown by Mathew *et al* to attenuate monocrotaline induced pulmonary hypertension, right ventricular hypertrophy, and pathological changes in the pulmonary vasculature in Wistar and Spraque-Dawley rats.[54] Abu-Osba *et al* showed in a placebo controlled study of anaesthetised and ventilated sheep that during induced hypoxia (by breathing 10% oxygen) a sharp increase in the mean (SD) pulmonary artery pressure occurred from 16 (2·8) to 26 (5·3) mm Hg.[55] During hypoxia there was no change in pulmonary arterial pressure (27 (5·7) mm Hg) after a placebo had been given. In contrast there was a sharp decrease after magnesium sulphate infusion (dose 200 mg/kg, serum concentration 2·88 mmol/l) in the right atrium; mean pulmonary arterial pressure was 25 (5·7) and 17 (5·6) mm Hg before and after treatment, respectively, $p<0·001$. There was no change in the cardiac output and a transient decrease in the heart rate.

In severely sick infants born at full term with persistent pulmonary hypertension of the newborn and who did not respond to conventional treatment for 46–72 hours, magnesium sulphate was used as a vasodilator, a muscle relaxant, and a sedative (YK Abu-Osba *et al*, abstract presented at Paediatric Research Society Meeting, Leeds, March 1989).[56] No other drugs were given or changes in the respirator settings or fractional inspiratory oxygen (F_IO_2) were made after the magnesium sulphate had been given unless oxygen tension rose; F_IO_2 and respirator settings were then reduced. Four infants had A-aDO$_2$ gradients of over 84·5, and one had an A-aDO$_2$ of 81·9 kPa, with predicted mortalities of 100% and 94%, respectively. After treatment with magnesium sulphate, mean (SD) oxygen tensions and haemoglobin oxygen saturation increased significantly within six hours from 4·3 (1·9) to 11·8 (7·6) kPa, $p<0·04$, and 58 (30) to 95 (5)%, respectively ($p<0·03$). One infant died with a persistent A-aDO$_2$ of over 84·5 kPa. None had intraventricular haemorrhage, bronchopulmonary dysplasia, or bradycardia requiring intervention.

These studies show that magnesium is beneficial in reducing hypoxia induced pulmonary hypertension in both animals and in full term infants with persistent pulmonary hypertension of the newborn. Its efficacy in preterm infants and for other non-hypoxic causes of pulmonary hypertension should be investigated. Some reports have described a beneficial vasodilating effect together with reduction of complications after ischaemic hypoxia in the central nervous system, heart, kidneys, and liver.[45 46–48] These conditions frequently coexist with pulmonary hypertension and severe hypoxaemia in neonates. Though a controlled multicentre large study is required before recommending magnesium as a first line of treatment, these studies suggest its possible benefits in persistent pulmonary hypertension of the newborn when conventional treatment has failed, is contraindicated, or is unavailable. Close monitoring of blood pressure, kidney function, glucose calcium concentrations should be undertaken. Long term follow up is needed.

I thank Professor RDG Milner for helpful discussion and criticism.

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PERINATAL LESSONS FROM THE PAST

Francois Mauriceau (1637–1709) and maternal posture for parturition

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Francois Mauriceau had an extensive practice in midwifery in Paris, both private and in the Hotel Dieu, which was at that time the leading establishment for lying in women in Europe. In 1668, when only 31, he published his great work *Traité des Maladies des Femmes Grosses et Accouchées*,[1] which according to André Levret 'drew from the cradle' the art of midwifery.[2] Two years later Mauriceau received a visit from Hugh Chamberlen, a member of the British family that possessed the secret of the obstetric forceps, who then translated his text making it available to the English speaking world. The influence of this work on many aspects of midwifery was immense,[3] and Mauriceau is still remembered eponymously for his description of delivery of the after coming head in breech presentation. Mauriceau's book also contains a section entitled 'Of children newborn and their ordinary Distempers, together with necessary directions to chuse a Nurse'. Among the 18 chapters are ones on 'Of cutting the Tongue when Tongue-ty'd' and 'How to cure the Venereal Lues in Infants'. Perhaps, though, in retrospect his greatest impact was in the influence his advice had on the position that women should adopt during delivery. From earliest times women throughout the world had usually assumed an upright posture during parturition. In Europe the birthing chair was particularly popular.[4] As Atwood has written[5]: 'The first major obstetrical change in the position of the parturient occurred when Francois Mauriceau substituted the bed for the birth stool. The time honoured 'position' assumed in an obstetric chair was replaced with the recumbent position to facilitate examinations and obstetric operations for the obstetrician'.

Let us study what Mauriceau actually wrote on this subject:

> 'The bed must be so made, that the woman being ready to be delivered, should lie on her back upon it, having her body in a convenient figure, that is, her head and breast a little raised, so that she be neither lying or sitting; for in this manner she breathes best, and will have more strength to help her pains, than if she were otherwise, or sunk down in her bed. Being in this posture, she must spread her thighs abroad, folding her legs a little towards her buttocks . . . and have her feet stayed against some firm thing; besides this, let her hold some persons with her hands, that she may better stay herself during her pains . . . bearing them down when they take her, which she may do by holding her breath, and forcing herself, as much as she can, just as when she goeth to stool . . .'.

Francois Mauriceau of Paris, 1637–1709.

The semirecumbent delivery position described by Mauriceau became known as the 'French' position and its use steadily spread throughout Europe and North America during the centuries that followed. Gradually in many countries it evolved into the fully recumbent or lithotomy position. More recently, with the diffusion of Western obstetrics, the dorsal position has also been introduced into many developing countries. Though some authors have credited Mauriceau with this change in delivery position,[3] others regard the dorsal recumbent posture to be the most mischievous intervention in modern obstetrics, causing parturition to be more drawn out, more painful for the mother, and less safe for the fetus.[6] To be fair to Mauriceau it should be recorded that he also recommended ambulation during labour, writing:

> '. . . she may walk about her chamber . . . The patient may likewise by intervals rest herself on her bed, to regain her strength; but not too long, especially little, or short thick women, for

they have always worse labours if they be much on their beds in their travail, and yet much worse of their first children, than when they are prevailed with to walk about the chamber, supporting them under their arms, if necessary; for by this means, the weight of the child, the woman being on her legs, causeth the inward orifice of the womb to dilate sooner than in bed; and her pains to be stronger and frequenter, that her labour be nothing near so long.'

Until recently I shared the belief that Mauriceau had introduced the dorsal recumbent position for delivery. Then, by chance, I came across the following passage in an 18th century English translation of Aristotle's *Experienced Midwife*, written around 350 BC:

'The bed ought to be ordered, that the woman, being ready to be delivered, should lie on her back upon it, having her body in a convenient posture; that is her head and breast a little raised so that she be between lying and sitting; for being so placed, she is best capable of breathing, and likewise will have more strength to bear her pains, than if she lay otherwise, or sank down in her bed. Being so placed, she must spread her thighs abroad, folding her legs a little towards her buttocks . . . and let her feet be staid against some firm thing; besides this let her take hold of some of the good women attending her with her hands that she may the better stay herself during her pains . . . bearing them down when they take her, which she must do by holding in her breath, and forcing herself as much as possible, in like manner when she goes to stool . . .'

Nobody comparing this excerpt with the earlier one cited from Mauriceau can remain in doubt that the latter lifted his recommendation on delivery position straight from Aristotle. The evidence is even stronger when it is remembered that both English texts had already been translated from either their original Greek or French. It was unfortunate that Mauriceau plagiarised Aristotle in this instance: for Hippocrates, Soranus of Ephesus,[7] and other classical authors all recommended an upright posture for parturition. Thus by strange chance, the disadvantageous dorsal position leapt two thousand years into post-renaissance Europe from its rare advocate in the distant past.

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BOOK REVIEW

Infectious Diseases of the Fetus and Newborn Infant. Third Edition. Edited by Jack S Remington and Jerome O Klein. (Pp 1122; £132·50 hardback.) W B Saunders Company (Harcourt Brace Jovanovich), 1990. ISBN 0-7216-2434-0.

I pleaded with the editors to be asked to review this book, even bargaining that I would agree to write an annotation on condition that I be allowed to review it. When I was first consulted on neonatal infections, Remington and Klein was a combination of Bible and 'suck rag', the all knowing comfort. It is a *tour de force*. The arrival of the third edition on my desk gave me an enormous thrill.

I was not disappointed. The book has been extensively updated, and every chapter contains references up to 1987 or 1988. There are new chapters on breast milk and on human immunodeficiency virus infection. Some chapters have new authors, and in almost all cases they are recognised leaders in their field. Major revisions have been made, encompassing technical advances, to the chapters on immunology (Christopher Wilson), cytomegalovirus (Sergio Stagno), herpes simplex virus (Richard Whitley), and obstetric factors (Ronald Gibbs): all are new authors in this book and their chapters are fresh and informative.

This edition is more practical than the previous two editions. For example, previously the recommendations for the management of illnesses like perinatal chickenpox and perinatal tuberculosis tended to be unreasonable and didactic ('separate mother and child, keep siblings away, and discharge home after two weeks') whereas they are now more humane and workable. Guidelines on the management of the baby whose mother has gestational syphilis are clear and practicable. I tried a few topical issues to see if they were covered: ureaplasma is thoughtfully discussed by Jerry Klein, human herpesvirus 6 is mentioned, hepatitis C virus caught the stop press. Imipenem and aztreonam are covered in the chapter on antibiotics. Surprisingly, there is virtually no mention of the use of intravenous immunoglobulins to prevent or treat neonatal infections.

This is an exhaustive book; there are at least 200 references for most chapters and 792 in the chapter on group B streptococcal infections. At times it is exhausting. The chapter on toxoplasmosis is still over 100 pages long and could have been shortened by half without substantial loss of content. But that weakness is also the book's strength. It is an invaluable reference book covering almost every aspect of neonatal infection, and is accessibly presented so that information can easily be found. Photographs are good, although graphics are underused.

I must not be churlish. No book is perfect, but this is as close to it as any medical reference book I know. All neonatologists need access to this book, which contains so much information not readily available elsewhere. There is enough new material since the second edition in 1983 to suggest you dig deep in your pockets (though not desperately deep by modern standards) and buy this excellent book.

DAVID ISAACS
Consultant paediatrician

Chromosomes galore

A fascinating review in *Developmental Medicine and Child Neurology* (Punnett and Zakai 1990;32:824–9) covers the chromosomal origins of nine syndromes. The syndromes that will be most familiar to paediatricians are the Prader-Willi, Angelman (happy puppet), DiGeorge, and Beckwith-Wiedemann. The first two of these are apparently caused by deletion of the same gene from the long arm of chromosome 15 (15q11^{-}). How come? Well it seems that if the missing bit is of paternal original you get Prader-Willi syndrome and if it's from the mother you have Angelman's syndrome. Neat, isn't it? The phenomenon of differential expression of apparently identical genetic material is called imprinting.

DiGeorge's syndrome, it seems, is associated with abnormalities of several chromosomes, including the long arm of chromosome 22 (22q11), and the short arms of chromosomes 10 (10p13) and 17 (17p13).

Beckwith-Wiedemann syndrome is associated occasionally with a visible duplication within the short arm of chromosome 11 (11p15). Family studies have indicated tight linkage to markers at 11p15, though DNA analysis has so far failed to demonstrate increased gene dosage at that site. Curiously all monozygotic twins with this syndrome have been girls and their twin sisters have been normal.

Alagille's syndrome (intrahepatic biliary hypoplasia, characteristic facies, mental retardation, and heart and vertebral defects) is associated with a deletion on the short arm of chromosome 20 (20p11).

The other syndromes are ones I haven't come across before—Miller-Dieker, Langer-Giedion, and Pallister-Killian, and the AGR triad. The Pallister-Killian syndrome is associated with a duplication (12p) and the others with microdeletions (17p, 8q, 11p).

The geneticist is king! Read Francis Crick's autobiography for an insight into how it all started.[1]

ARCHIVIST

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[1] Crick F. *What mad pursuit: a personal view of scientific discovery.* New York: Basic, 1988.

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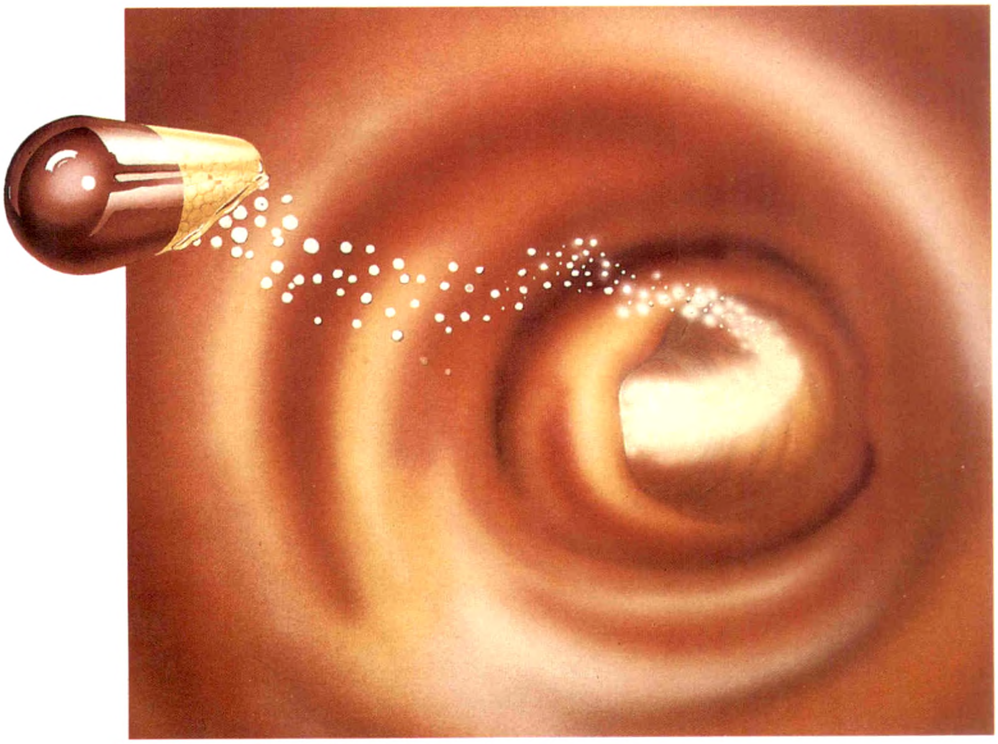

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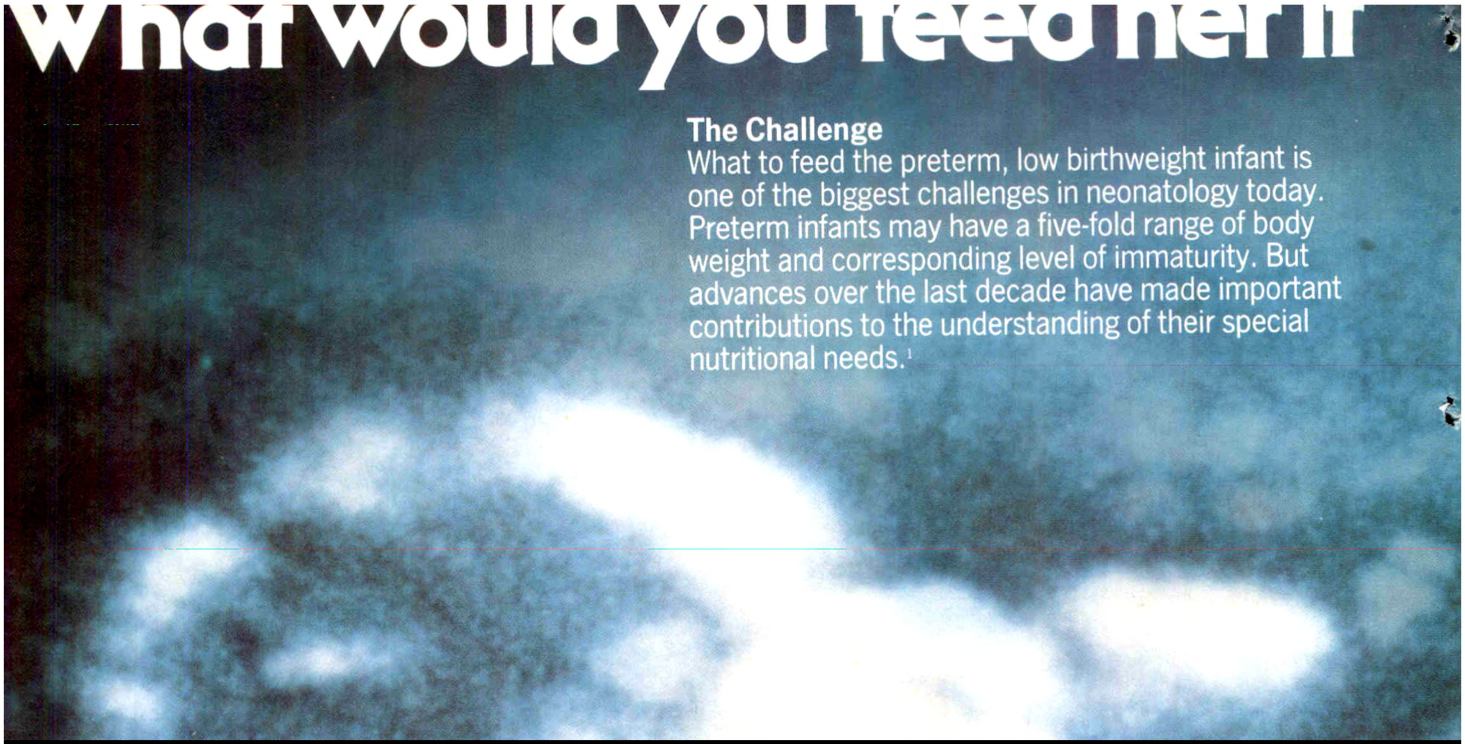

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1 Anonymous. Writing economically. *Arch Dis Child* 1990;65:251.

Annotations

Asperger's syndrome

In 1944 the Viennese paediatrician, Hans Asperger, described a group of children with what he called 'autistic psychopathy of childhood'.[1] He was in no doubt that this was a long lasting personality disorder, affecting predominantly boys, and he outlined its features as follows:

- Solitariness
- Abnormalities of gaze, expression, and gesture impeding emotional contact with other people
- Insensitivity to social cues
- Lack of feeling for others sometimes amounting to callousness
- Oversensitivity and insensitivity
- 'Autistic intelligence': inventive rather than imitative, with specific interests in restricted fields such as chemistry, poisons, mathematics, or art which could lead to creative achievements
- Educational delays of all kinds
- Rage or tears in the face of pressure to conform.

With age, social adaptation often improved and the work adjustment of gifted autistic psychopaths was good, but their basic personality features endured and intimate relationships remained impaired. Sexual interests were often meagre and occasionally deviant.

While Asperger considered the condition as possibly preschizophrenic, apparently only two of the 400 such cases he saw subsequently developed this illness.[2] In every case one or more biological relatives were affected with the full or partial syndrome. In later years, Asperger drew a firm distinction between his 'autistic psychopathy of childhood' and Kanner's early infantile autism and he described the children, who differed from any he had seen before, as 'highly intelligent children with interesting peculiarities, yet never the less with behaviour so difficult that they were almost impossible to keep in family or school . . . They achieve the highest university professorships or become artists—yet their quirks and peculiarities will remain with them for life'.[3]

Two developments in diagnostic practice have occurred since then. Lorna Wing[4] and Digby Tantam[5] studied groups of seriously impaired children and adults (of whom only two out of 60 had married and only one had been in continuous employment since leaving school) with the features Asperger had described and found that many of their patients had had the symptoms of early infantile autism or of autism beginning in later childhood. Wing described the salient features as a failure in two way social interaction, difficulty in verbal and non-verbal communication, and impaired imagination, and she coined the diagnostic label 'Asperger's syndrome'. This she held to be equivalent to high level autism (that is with normal intelligence and no gross early language delays). The concept of an 'autistic spectrum' derives from this work.[6 7] Wing's criteria were also used by Gillberg to clarify the similarities between Asperger's syndrome and infantile autism.[8]

The second development arose from the identification of a group of children referred to a psychiatric clinic who described themselves or were described by others as 'loners'. They had the features of schizoid personality disorder as recorded in the older psychiatric literature (perhaps not altogether familiar to Asperger, the paediatrician). They too, while much less impaired than the cases reported by Wing and Tantam, were like the children Asperger had described. Their personality characteristics were very long lasting,[9] and more recent studies showed three quarters of them to fulfil the American diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders,* DSM-III) for schizotypal personality disorder which is part of the schizophrenia spectrum (S Wolff *et al*, to be published). The main, and enduring, features of these subjects were solitariness, impaired empathy and emotional detachment, increased sensitivity, at times with paranoid ideation, circumscribed interest patterns, and unusual styles of communication. In childhood, a very few resembled but were in fact never diagnosed as autistic children. A very few were electively mute, but most of them presented with the features of schizoid personality itself, with educational difficulties or with the kind of conduct or mixed conduct and emotional disorders usually regarded as secondary to adverse life experiences. Specific developmental delays, including delays of language related skills, were much commoner than in other referred children (S Wolff, to be published). The schizoids were predominantly boys (ratio 4:1), were of slightly above average IQ; and came from an upwardly skewed social class background. Referral took place during the school years and the main difficulty was often an apparently inexplicable failure to conform to the ordinary demands of school life. Aggressive outbursts and pathological lying were occasional features. With few exceptions these children were regarded as 'awkward' rather than handicapped.

Special school arrangements allowing for greater privacy and reduced pressure to conform were helpful, as was the acceptance of the children's difficulties as constitutional: neither wilful nor parent engendered. In later life, many of them had good work achievements and many married, but their overall work adjustment, their heterosexual adjustment, and their psychiatric state were worse than those of other referred children grown up (S Wolff, to be published).

These children resembled the schizotypal children described by Nagy and Szatmari,[10] and their difficulties certainly overlapped with those of the patients of Wing and Tantam. But whether they too should be included in an 'autistic spectrum' will depend on the results of more definitive genetic studies.

For this reason, the arguments put forward by Professor Cox in this issue against a global diagnosis of autism,[11 12] and in defence of a distinct diagnostic category of Asperger's syndrome, although based on Wing's rather narrow definition, are to be welcomed.

Dorothy Bishop, like other workers, considers Asperger's syndrome to overlap both with autism and with specific developmental language disorders, often diagnosed as congenital dysphasia.[13] A number of children with these disabilities also have the social impairments of Asperger/schizoid disorders. She suggests a two dimensional model for autistic type disorders, with impaired meaningful verbal communication on one axis and impaired social relationships with circumscribed interest patterns on the other. Asperger's syndrome, on this model, would overlap both with autism and with specific language disorders, but would be characterised by low scores on the language disorder dimension and high scores on the social impairment/circumscribed interests dimension.

Work on the diagnosis of these disorders is of theoretical interest, especially in disentangling the causal factors involved. It is also of great clinical importance. Children with severe forms of Asperger's syndrome will need the same services as well functioning autistic children. The more intelligent and less obviously handicapped Asperger/schizoid children require above all to be identified as constitutionally impaired.[14] Their special make up needs to be understood. They may also need special arrangements made, particularly at school, in the knowledge that in later life when pressures for conformity are less than during the school years, many will be able to find their social niche, and a few to develop their rather exceptional gifts.

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Possible aetiological factors in childhood leukaemia

Leukaemia accounts for over half of all cancers diagnosed in children, with one in 2000 developing the disease before their 15th birthday.[1–3] Despite considerable improvements in treatment over the last 20 years, about half of those who develop childhood leukaemia die within five years of diagnosis. Speculations about the causes of leukaemia in children abound, and several new and exciting theories have recently been suggested.

Ionising radiation

Exposure to ionising radiation is known to cause leukaemia.[4 5] Furthermore, the fetus and young child seem to be more susceptible to the effects of ionising radiation than the adult.[6–9] The controversial suggestion of Stewart *et al*, made in 1958, that prenatal exposure to *x* rays might increase the risk of childhood leukaemia has taken several decades to settle. It is now widely accepted that as much as 5% of all childhood leukaemias could be caused by diagnostic radiography of the mother's abdomen while the child is in utero.[7–10]

Today, the possible contribution of natural radiation is a controversial topic. Estimates of the proportion of all childhood leukaemias attributable to background radiation range from a few percent to nearly all.[7 11–13] Assumptions about the relative effects of external gamma radiation and internal alpha particles on children of different ages and babies of different gestations alter these estimates appreciably.[7 11] Discussion has intensified recently after the report by Dr Henshaw and his colleagues demonstrating a correlation between indoor radon levels in different countries and the incidence of leukaemia and other cancers in children.[12] They suggest that a sizable proportion of all childhood leukaemias could be caused by exposure to radon gas in the home. These issues are now being vigorously investigated, but at this stage the aetiological relevance of natural background radiation is unclear.

More controversial still is the hypothesis that germ cell mutations induced by ionising radiation might increase the risk of leukaemia in the progeny of those exposed. This suggestion comes from the investigations of Professor Gardner and his colleagues of the raised incidence of childhood leukaemia near the Sellafield reprocessing plant in West Cumbria.[14] They found that exposure of fathers at work to comparatively low doses of external ionising radiation was associated with an increased risk of leukaemia in their offspring. The main finding of a sixfold to eightfold excess in the children of those most heavily exposed is, however, based on only four cases. As well as exposure of fathers at work to ionising radiation, other explanations are possible.[14–18] For example, external gamma radiation may not be the relevant exposure and exposure at work to other harmful agents may be involved. In particular, it has been hypothesised that radionuclides may accumulate in the male reproductive organs. Such a mechanism could explain both the high mortality from prostatic cancer found in highly exposed nuclear workers, and the increased incidence of leukaemia in the offspring of radiation workers at Sellafield.[16 17] Mothers' exposure to radiation before and during pregnancy may also be important, and could occur if contaminated clothing or equipment were brought home from the place of work.[14–18] Two studies, similar to that of Gardner et al, of leukaemia and non-Hodgkin's lymphoma in the vicinity of nuclear establishments are in progress in the United Kingdom. One is taking place around the United Kingdom Atomic Authority plant of Dounreay and the other around Atomic Weapons Establishments at Aldermaston and Burghfield. These should help to clarify the relation between childhood leukaemia and parental employment in the nuclear industry.

Infectious disease

There has been considerable speculation about the possible aetiological role of infectious diseases.[4 5] Initially, after the identification of leukaemogenic viruses in animals, similar human viruses were sought. Despite intensive investigations, no specific human virus has been identified and interest has shifted to the possible effects of common viruses. The suggestion is that childhood leukaemia results as a rare response to a common, possibly sublinical, infection.[19–21] More specifically, Greaves has hypothesised that the immune response itself promotes the development of leukaemia by inducing proliferative stress in bone marrow lymphocyte precursors, thus increasing the risk of spontaneous mutations.[19 20] Indirect support for the involvement of infectious agents comes from the characteristically sharp peak in incidence of the common childhood form of acute lymphoblastic leukaemia that occurs at around 3 years of age. This is the age when many children first begin to attend playgroup and school, and for some children this would result in their first significant exposure to infection. Reports that childhood leukaemia may be more common in higher social classes and in first or only children suggests that susceptibility may be similar to the polio model.[4 5 19 20] Kinlen has further hypothesised that isolation and migration might be important, and has suggested that children living in isolated rural communities who come into contact with individuals from more urban areas might be at increased risk.[21] Despite its appeal there is still no direct evidence to support the infectious disease hypothesis in humans, but this topic continues to be the subject of intensive research.

Drugs

Apart from ionising radiation, chemotherapy is the only other established cause of leukaemia. Its contribution to the total amount of childhood disease is, however, small as it has been shown to increase the risk of acute myeloid leukaemia only, which is rare in children.[4 5] Other drugs recently mooted to cause childhood leukaemia include the antibiotic chloramphenicol[22] and more recently in utero exposure to marijuana.[23]

Other chemical and physical exposures

Exposure of parents both at work and at home to a number of potentially toxic chemicals have been suggested as risk factors for childhood leukaemia. Most epidemiological investigations of parental exposure have, however, been based on small numbers and on information collected routinely at death or cancer registration. To date, the evidence supporting an association between childhood leukaemia and compounds such as benzene and lead is weak and contradictory.[22 24]

Non-ionising electromagnetic radiation has also been suspected as increasing the risk of leukaemia and other cancers. Particular concern has been expressed about residence near power lines and use of electric blankets.[25 26] Again, the epidemiological evidence is inconsistent and the data are difficult to interpret, mainly because of the lack of reliable measures of exposure.

Chromosomal anomalies

About 3% of all childhood leukaemias are associated with recognisable chromosomal disorders, such as Down's syndrome, Klinefelter's syndrome, and Fanconi's anaemia.[4 5] In these congenital or hereditary syndromes, the chromosomal abnormality appears to place the individual at increased risk of disease. For the majority of leukaemias, however, the significance of the chromosomal abnormalities found in all leukaemic cells is unclear.

Conclusion

Leukaemia is the major paediatric malignancy of developed countries. Recent advances in the treatment of childhood leukaemia have not been matched by similar advances in the understanding of its aetiology. At present, ionising radiation and chemotherapy are the only established causes of leukaemia, although many other plausible hypotheses remain.

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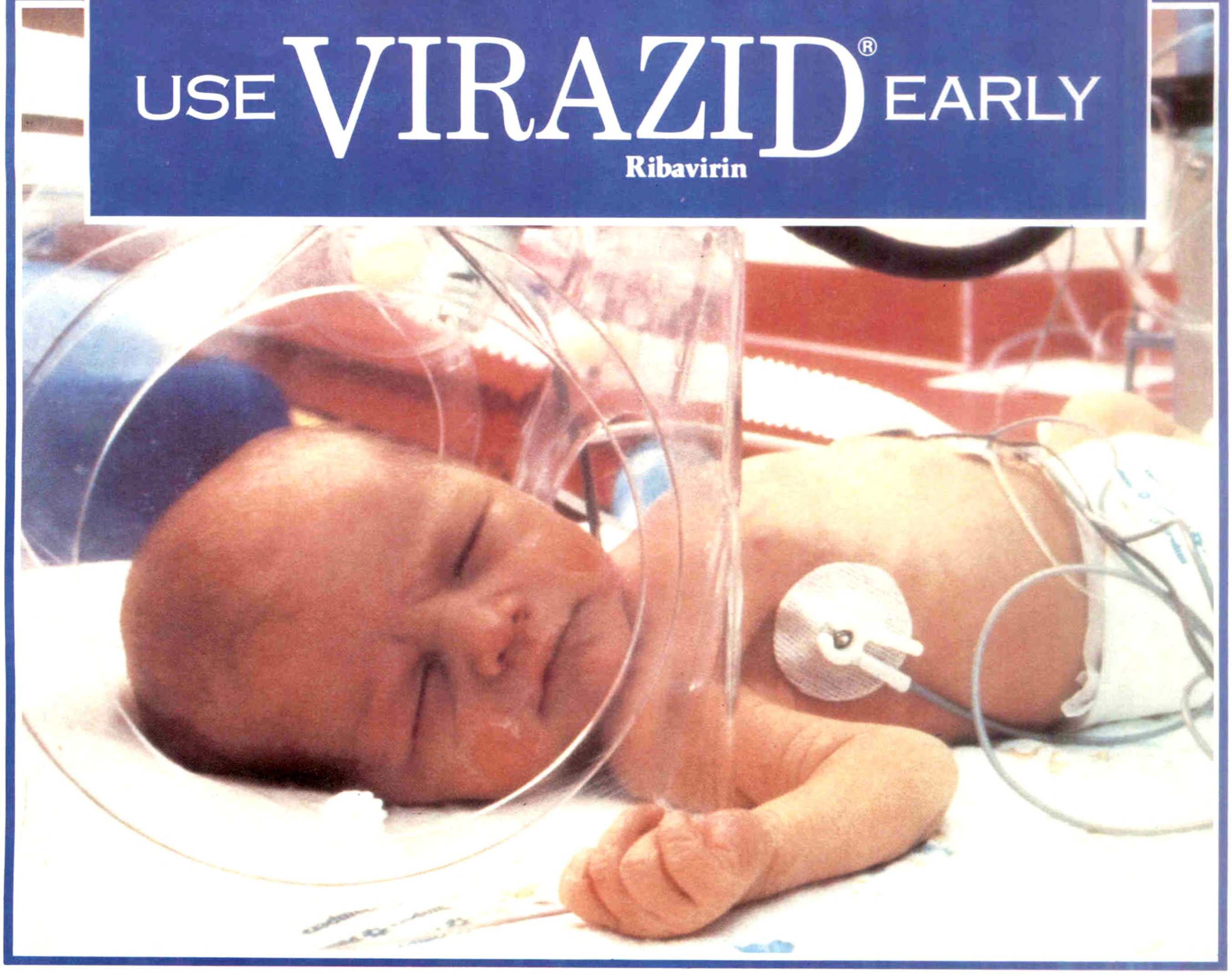

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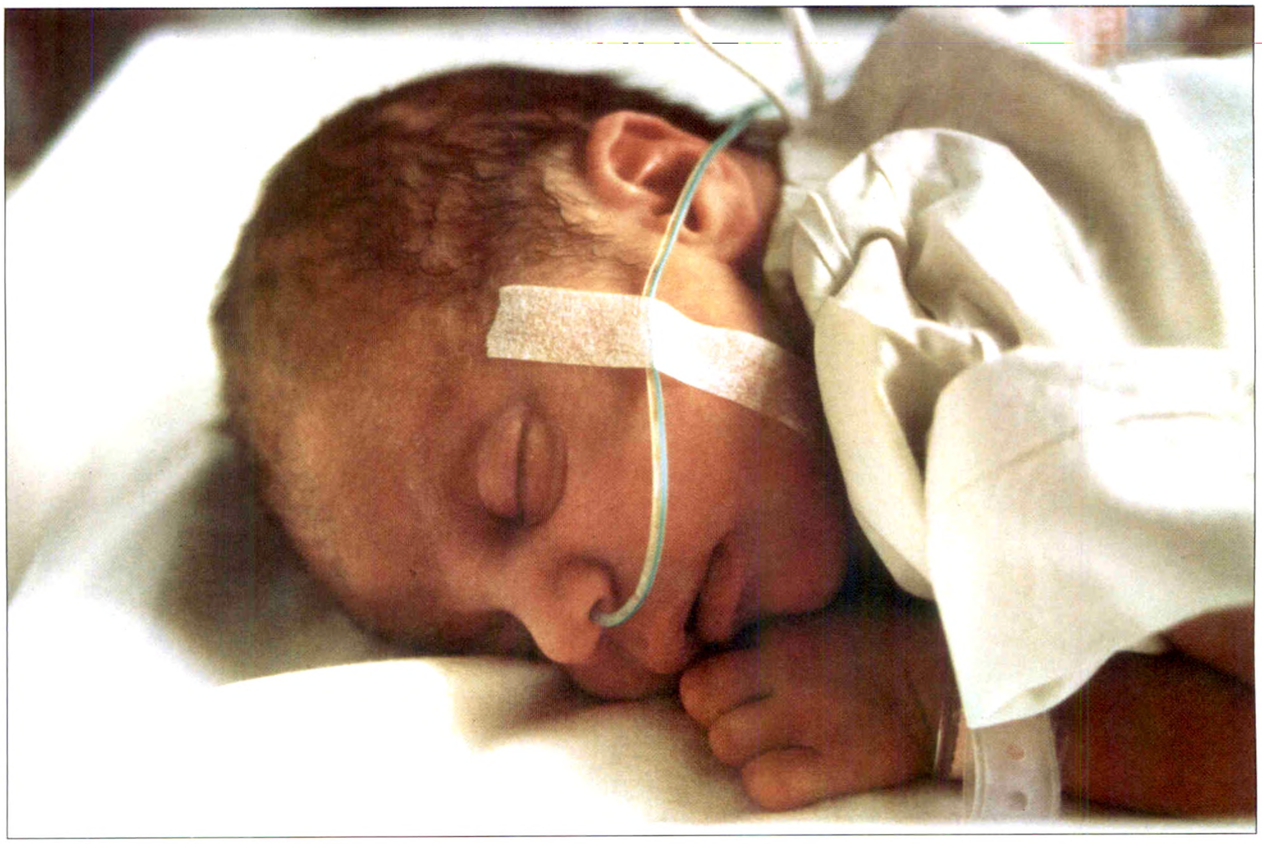

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ORIGINAL ARTICLES

Endotoxin induced damage to the cochlea in guinea pigs

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Abstract

An apparently unique form of cochlear damage was produced in guinea pigs by perfusing the cochlea or injecting the cerebrospinal fluid with bacterial endotoxin. This developed rapidly (within two hours) and was characterised by swelling of the tectorial membrane and damage to both inner and outer hair cells, with parallel functional damage demonstrable electrophysiologically. All these changes could be attenuated by pretreatment with dexamethasone. Such endotoxin mediated lesions may be the mechanism by which hearing loss occurs in bacterial meningitis.

Deafness is a well recognised complication of bacterial meningitis. Ten per cent or more of children who contract bacterial meningitis develop significant sensorineural deafness,[1 2] and it is the most important cause of acquired permanent deafness in children.[3] The mechanism by which deafness is produced has not been clearly defined. Recent studies have shown that most of the other clinical characteristics of meningitis can be produced by bacterial cell wall material alone—endotoxin in the case of Gram negative organisms and lipoteichoic acid in the case of the Gram positive *Streptococcus pneumoniae*.[4 5] Endotoxin itself is relatively harmless to most mammalian cells in vitro and is thought to act in vivo by provoking the release of cytokines such as tumour necrosis factor and interleukin-1, which themselves initiate the inflammatory response.[6 7] This release of cytokines can be suppressed by dexamethasone.[8] Because so many of the other features of bacterial meningitis result from the inflammatory response to endotoxin, we wondered whether the hearing loss that so commonly occurs could be accounted for similarly.

Methods

After urethane anaesthesia and tracheal cannulation in the guinea pig the left temporal bulla was exposed and a round hole approximately 50 μm in diameter was drilled into the basal turn of the scala tympani, about 2 mm from the round window. A slightly larger hole was made at the tip of the cochlea to allow the perfusate to flow out. A glass micropipette filled with artificial perilymph and linked to a 'Treonic' microinfusion pump (IP-3, Vickers Medical) was inserted into the basal hole in the scala tympani and fitted tightly into it. Artificial perilymph containing endotoxin (*Escherichia coli* 026:B6 lipopolysaccharide (Sigma Chemicals), 100 ng-1 μg) was introduced into the cochlea in a total volume of 17 μl over a period of one minute. Some leakage occurred from the apical hole, and this was mopped up with a tissue wick.

Recordings of cochlear microphonics and compound action potentials were made at 30 minute intervals for at least two hours using an electrode sealed within the glass micropipette.[9]

At the end of the experiment the cochlea was immediately fixed by intravital perfusion of glutaraldehyde and prepared for scanning electron microscopy as previously described.[10] The opposite cochlea was similarly fixed immediately after death. These studies were repeated after pretreatment of the guinea pigs with dexamethasone (1 mg/kg intraperitoneally) one hour before the infusion of endotoxin. Similar experiments were performed in which 100 ng-1 μg of *E coli* endotoxin were injected intracisternally into the cerebrospinal fluid. These studies too were repeated after pretreatment with dexamethasone. Control studies were performed perfusing the cochlea with artificial perilymph alone, without endotoxin. Each experiment was repeated several times.

Results

Administration of endotoxin directly into the scala tympani has shown that sound evoked

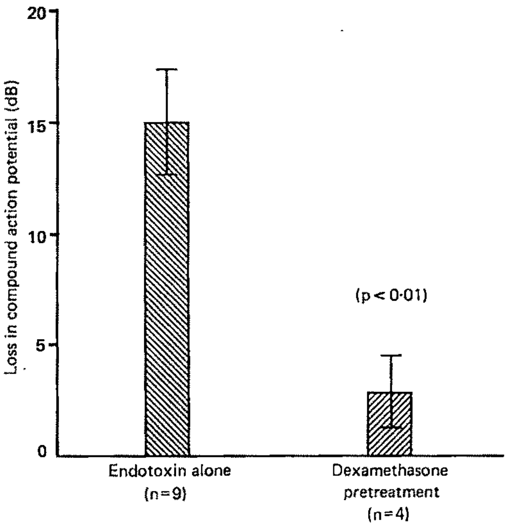

Figure 1 Mean increase in intensity of tone pip (expressed as dB loss) required to restore the compound action potential to pretreatment height in nine guinea pigs treated with endotoxin alone and in four animals pretreated with dexamethasone. The bars indicate mean (SEM).

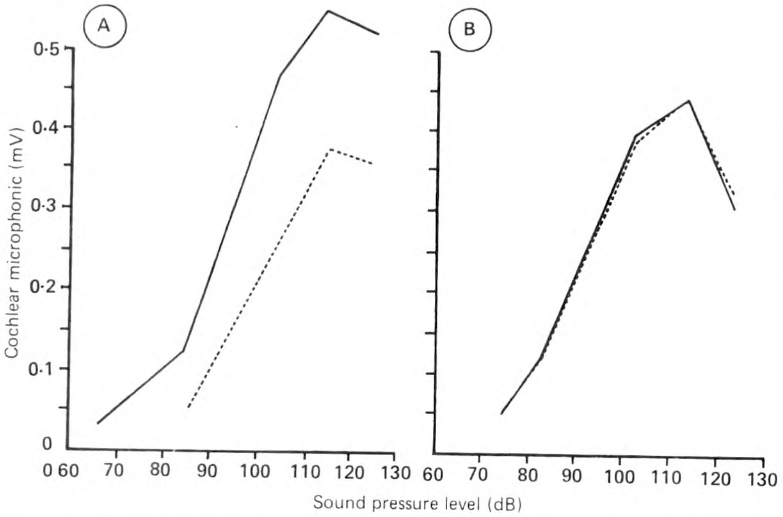

Figure 2 (A) Relationship between peak to peak height of the cochlear microphonic and intensity of stimulus (5 kHz tone). Solid curve is the normal pretreatment response. Broken line is the response two hours after perfusion of endotoxin into scala tympani. (B) as (A) except that the guinea pig was pretreated with dexamethasone. Solid line is the normal response before endotoxin perfusion. Broken line is the response two hours after perfusion with endotoxin.

electrical responses such as compound action potential and the cochlear microphonics are affected. In our experiments the compound action potential was elicited by stimulation with a 1 msec 10 kHz tone pip.

The amplitude of the first negative wave (N1) of the complex represents the synchronous activation of primary auditory nerve fibres by the stimulus and is thus a measure of cochlear output. Administration of endotoxin produced a consistent drop in the size of the compound action potential; the extra intensity of sound necessary to return the amplitude to its original value was measured, and expressed in decibels (dB). Readings were taken at half hourly intervals up to a maximum of 2·5 hours.

In most cases no change was seen in the first hour after the endotoxin administration but thereafter there was a marked drop in the height of the response (fig 1). By contrast, the endotoxin caused a fall in the height of the cochlear microphonic (an electrical response of the hair cells alone) starting in most cases in the first half

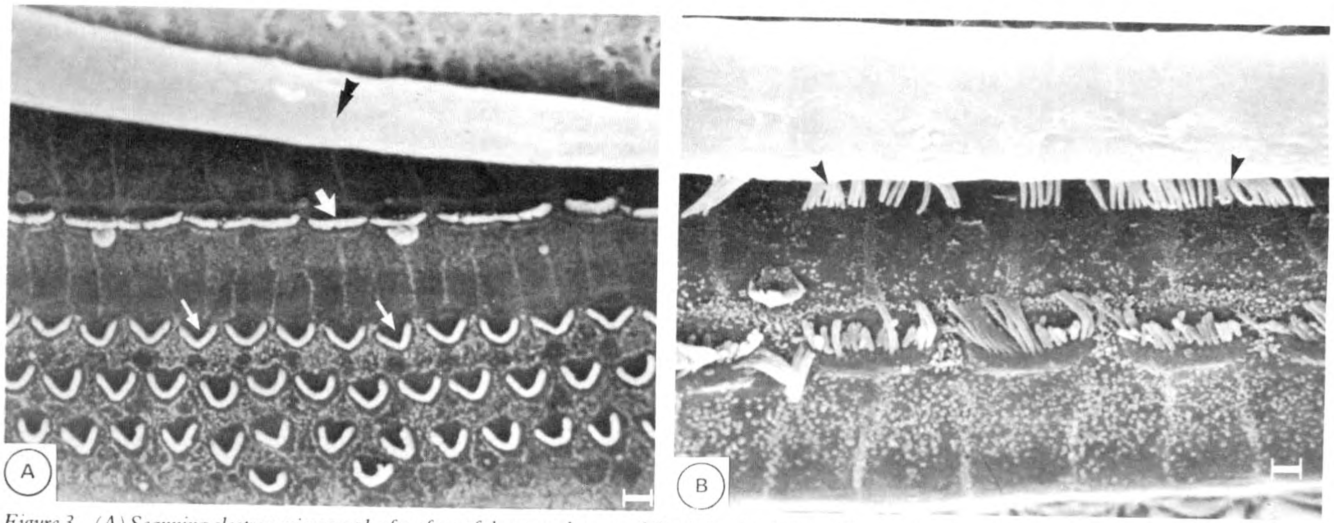

Figure 3 (A) Scanning electron micrograph of surface of the normal organ of Corti showing hair bundles of inner (broad white arrow) and outer hair cells (thin white arrows). Double black arrow head indicates the tectorial membrane. Scale bar: 5 µm. (B) as (A) but two hours after endotoxin perfusion. Note stereocilia of inner hair cells are adhered to the tectorial membrane (black arrow head). Hair bundles show severe disruption. Scale bar: 2 µm.

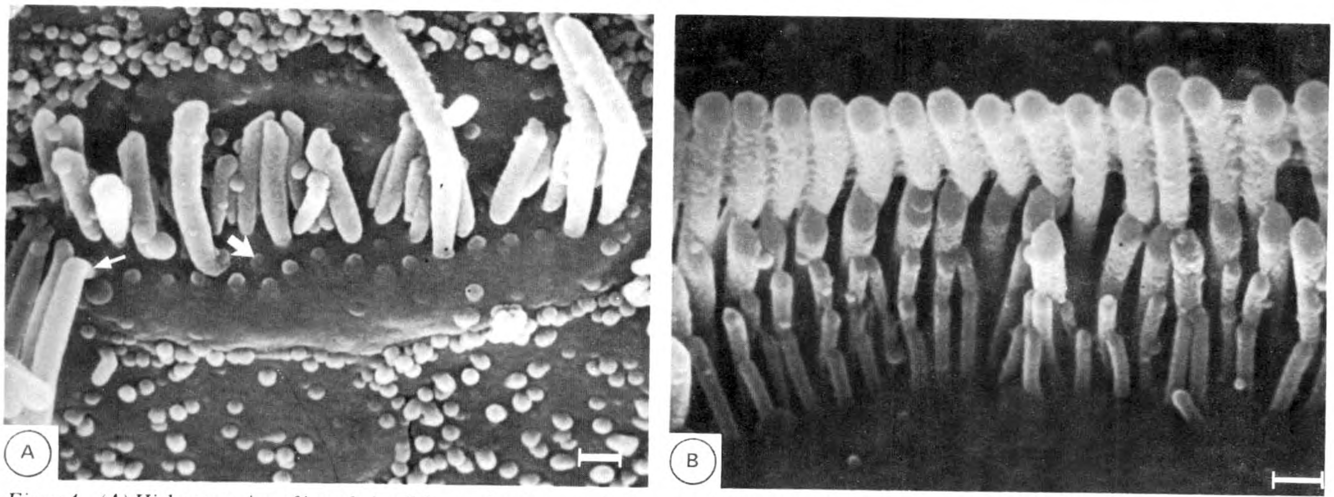

Figure 4 (A) High power view of inner hair cell from endotoxin treated guinea pig. Many stereocilia are missing having been torn from their roots (thick white arrow). Other stereocilia are kinked (thin white arrow). Scale bar: 500 nm. (B) as (A) but guinea pig pretreated with dexamethasone. Hair bundle of inner hair cell shows good preservation and organisation of stereocilia. Scale bar: 500 nm.

hour and continuing for the remainder of the experiment (fig 2). Perfusion of the cochlea with artificial perilymph alone showed no significant change in compound action potential or cochlear microphonics, and no detectable ultrastructural alteration to hair cell morphology.

When guinea pigs were pretreated with dexamethasone the electrophysiological impairment produced by endotoxin was considerably reduced (figs 1 and 2). Two main morphological changes were noted in the cochlea after endotoxin treatment alone: the first was a generalised swelling of the tectorial membrane that frequently touched the stereocilia of inner hair cells—this does not occur in the normal cochlea. The second effect was damage to hair bundles of both inner and outer hair cells. Mild damage led to splaying of stereocilia; more serious damage was associated with kinking or bending of stereocilia, which were sometimes completely flattened so that they lay on the surface of the hair cells. Occasionally stereocilia were torn from their attachment on the hair cells and adhered to the tectorial membrane (fig 3). Pretreatment with dexamethasone reduced the severity of this damage (fig 4).

Essentially similar electrophysiological and ultrastructural changes occurred whether the endotoxin was introduced directly into the cochlea, or injected intracisternally into the cerebrospinal fluid, although the changes after intracisternal injection were more variable. In some guinea pigs treated with intracochlear endotoxin, hyperaemia of the brain surface was noted after two hours. No similar effect was observed in the animals treated with dexamethasone.

Discussion

A pronounced reduction in cochlear output, reflected both in compound action potential and in cochlear microphonics, occurred in guinea pigs within two hours of the microperfusion of endotoxin into the scala tympani. This was accompanied by ultrastructural changes to the stereocilia of both inner and outer cochlear hair cells, which seem to be characteristic of endotoxin induced damage and some of which (adherence of stereocilia to tectorial membrane) have not to our knowledge been reported in association with any other type of cochlear insult.

This effect can confidently be attributed to the endotoxin rather than the mechanical interference, because neither the surgical procedure nor the perfusion of artificial perilymph alone produced any ultrastructural or electrophysiological changes in the cochlea. Previous studies similarly confirmed that the procedure itself does not affect cochlear function.[11 12] In addition, intracisternal injection of endotoxin without any mechanical interference to the cochlea produced similar ultrastructural damage.

The morphological changes that we saw were sufficient in themselves to account for the electrophysiological losses that we detected, as hair cell stereocilia are essential for the transduction process that converts sound waves to electrical impulses.

A direct connection (the cochlear aqueduct) exists between the cerebrospinal fluid and the perilymph; this is patent both in guinea pigs[13] and in humans.[14] Bacterial endotoxin might well reach the inner ear in meningitis by this route. Consistent with this concept is the appearance of white cells in the perilymph rather than the endolymph, both in association with human meningitis[15] and with experimental meningitis in rodents.[16]

The auditory lesion leading to deafness in meningitis has up till now not been clearly defined. Most workers consider that it is likely to be cochlear,[17] but auditory nerve damage has not been ruled out, and no specific site of cochlear injury has been found. Our work would suggest that the cochlear hair cells may be the primary site of this hearing damage, and may be particularly vulnerable to the effects of endotoxin; other sites of damage within the cochlea cannot, however, be excluded. Cochlear damage is also consistent with the well recorded association between deafness in meningitis and associated vertigo or labyrinthitis,[18] and with the electrophysiological studies that have been performed on children left deaf after meningitis.[19 20]

Our findings also suggest a potential mechanism by which hearing loss can be limited in bacterial meningitis. Lebel *et al* and Girgis *et al*, in a series of well controlled clinical studies, found that steroids (used as adjuncts to antibiotics) improved the prognosis in children with meningitis.[21–23] The most pronounced effect that they found was the reduction of deafness in the steroid treated patients. Pretreatment of patients with meningitis with steroids is not a practical proposition, but it is of interest to note that until antibiotic treatment is started endotoxin concentrations in the cerebrospinal fluid both of experimental animals and of patients with meningitis remain relatively low, only rising rapidly in association with bacterial cell wall lysis.[24 25] Thus treatment with steroids starting at the same time as the antibiotic treatment may be sufficient to block much of the cochlear damage.

This concept is supported by the recent findings of Mustafa *et al* who showed that steroids reduced inflammation if given with (or before) antibiotics in experimental meningitis, but had little effect if their administration was delayed for one hour after the antibiotics had been given.[26]

The concentration of endotoxin present in the perilymph was difficult to assess accurately because much of it leaks rapidly out of the cochlea immediately after infusion, but as only 100 ng were sufficient to produce a clear effect despite this leakage, it seems likely that the effect we have described mimics that in natural infection and in experimental meningitis in rabbits, in which doses of 20 ng have produced a considerable inflammatory response.[27] The maximal loss of cochlear response was noted within two hours of the onset of perfusion with endotoxin. This time course fits in well both with the inflammatory effect noted in experimental meningitis in the rabbit when endotoxin was injected into the cerebrospinal fluid, and with the associated release of tumour necrosis factor.[6]

If this inflammatory process is mediated by cytokines their site of origin is unclear. It is possible that they are released from known cytokine producing cells in the central nervous system, such as astrocytes or microglia.[28 29] If this is the case, endotoxin would have been expected to gain access to the central nervous system through the cochlear aqueduct after cochlear microperfusion, and the cytokines to have diffused back in a similar manner. It is not impossible that the cytokines were released locally within the cochlea, especially as early evidence of hearing damage (within 60 minutes) was detected after local microperfusion.

Although we have shown a modulating effect of dexamethasone on cochlear damage induced by endotoxin, other anti-inflammatory drugs may have a similar effect and may have a role in the control of the inflammatory response in the ear.

We conclude that this endotoxin mediated effect may be the primary mechanism by which deafness is produced in meningitis, and that it may be possible to ameliorate this with drugs.

We thank Dr George McCracken for his advice and encouragement throughout this study, and Mr T Hayward for expert technical assistance.

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Clinical aspects of 100 patients with Kawasaki disease

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Abstract

We report 101 episodes of Kawasaki disease in 100 patients seen over a 12 year period. A total of 35 patients had cardiac involvement ranging from pericardial effusion to coronary artery aneurysms with ischaemic complications, which resulted in death in one patient. Laboratory investigations showed leucocytosis, thrombocytosis, and a raised erythrocyte sedimentation rate to be common features and the first two variables were significantly associated with cardiac involvement. Treatment regimens changed over the study period. Aspirin was used in most patients often in conjunction with dipyridamole and from 1986 intravenous immunoglobulin was given routinely to those patients seen early in the illness. Additional therapeutic measures in individual patients included prostacyclin, heparin, streptokinase, and plasma exchange/exchange transfusion. Attention is drawn to the uncertainty of the long term cardiovascular consequences in the light of adults reported with premature atherosclerotic lesions of similar appearance to those seen in Kawasaki disease.

Mucocutaneous lymph node syndrome or Kawasaki disease was first described in 1967 by Tomisaku Kawasaki.[1] This systemic vasculitis of childhood has since affected over 80 000 children in Japan. Its importance is the predilection for involvement of the coronary arteries in about 20–40% of cases, which in a small number may lead to coronary thrombosis, myocardial infarction, and death.

In the United Kingdom, as in other European countries and the United States, far fewer cases have been reported than in Japan. The British Paediatric Surveillance Unit (BPSU) started an active reporting system in 1986 and since that time the number of reports have increased but still only to about 70–90 cases per year.[2] Although this may be due to racial influences, it may in part also be due to a lack of awareness of the disease coupled with the absence of a diagnostic laboratory test.

In view of the relatively large number of patients with Kawasaki disease referred to this hospital and the lack of published data on the disease from the United Kingdom we have undertaken a retrospective review of our experience. Clinical details were obtained from the case files. In the majority the data was adequate but in some patients who had been referred only for echocardiography details were occasionally limited.

Patients and methods

PATIENTS

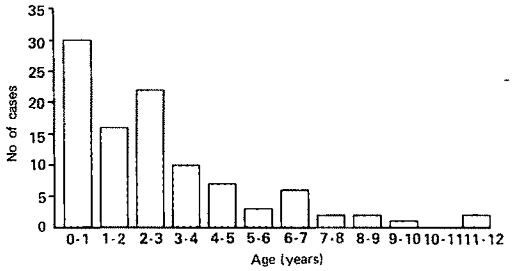
One hundred patients were referred to the Hospital for Sick Children over a 12 year period from 1977 to 1989. One patient had a relapse seven years after the initial episode, therefore 101 cases were analysed. Eighty children had been referred for management and advice and a further 20 for echocardiography only.

The diagnosis of Kawasaki disease was normally based on the presence of five of six of the established clinical criteria (table 1) or the presence of four criteria if coronary artery aneurysms were demonstrable. In some patients referred for echocardiography only, a diagnosis of Kawasaki disease had been made on apparently good evidence at the referring hospitals and despite the relatively inadequate clinical history these patients were included in the analysis.

There were 56 boys and 44 girls giving a ratio of 1·27:1. The age range was 0·25–11·9 years with a mean of 2·83 years and median of 2·2 years. The peak incidence occurred in the 0–1 year age group (figure).

The annual incidence increased over the period of study but there were no major fluctuations from year to year. More cases were admitted in the spring and early summer and there was an ethnic preponderance of Oriental and Afro-Caribbean relative to their presence in the general population (table 2).

Of the diagnostic criteria (table 1) fever of more than five days' duration was present in



Age at presentation with Kawasaki disease.

Table 1 Diagnostic clinical criteria for Kawasaki disease

(1) Presence of fever for >5 days
(2) Mucosal inflammation including sore/cracked lips, injected pharynx, or strawberry tongue
(3) Lymphadenopathy
(4) Polymorphous exanthema
(5) Bilateral conjunctivitis
(6) Characteristic changes in the peripheries: erythema of the palms and soles, desquamation of the fingers and toes, and peripheral non-pitting oedema

Table 2 Nationality of patients

	% Cases of Kawasaki disease	*% In United Kingdom*
White	54	
Oriental	12	1
Afro-Caribbean	21	2
Indian subcontinent	6	4
Other	6	
Unknown	1	

Table 3 Symptoms

	No of cases
Fever	100
Rashes	99
Lymphadenopathy	98
Mucosal inflammation	88
Peripheral changes	84
Conjunctivitis	80

nearly all cases. Next in frequency came polymorphous exanthemata most often a morbilliform maculopapular rash with widespread involvement of the trunk and extremities. Lymphadenopathy was common, including patients in whom enlarged nodes were noted but not necessarily measured. Changes in the mucous membranes involved injected and dry cracked lips in addition to pharyngeal injection and strawberry tongues. Peripheral extremity manifestations included peripheral oedema and erythema and in most cases there was a history of desquamation of the fingers and/or toes. Conjunctivitis was noted in 80 cases and was bilateral and non-purulent (table 3). Fifty four cases satisfied six criteria, in 30 five were met, in 15 four, and in one case only three diagnostic criteria were recorded.

CARDIOVASCULAR FINDINGS

A total of 35 cases had cardiac manifestations including 18 cases who had coronary artery aneurysms (most, but not all of these patients have had their coronary artery lesions described in the companion paper[3]). The non-aneurysmal cardiac complications included dilatation of the coronary artery in 12, pericardial effusion in four, abnormalities seen on electrocardiography suggesting ischaemia in seven, pericarditis in two, myocardial infarction in two, and myocarditis (with raised cardiac enzymes), left ventricular aneurysm, thrombus within aneurysm, mitral incompetence, and cardiac failure in one case each. Cardiac complications occurred more frequently in the younger patients and the median age of those with cardiac involvement was 1 year compared with 2·2 years for the whole group, but there was no preponderance of either sex.

OTHER SIGNIFICANT FINDINGS

In 81 cases in whom more detailed information was available there were a number of other symptoms or clinical findings recorded. These are detailed in table 4.

LABORATORY INVESTIGATIONS

Most patients showed evidence of an acute

Table 4 Other significant findings (n=81)

	No (% of case
Irritability	41 (51
Diarrhoea	27 (33
Vomiting	18 (22
Joint pain and tenderness	18 (22
Preceding upper respiratory tract infection	10 (12
Hydrops of the gall bladder	9 (11
Pneumonia	2 (2)
Abnormality on electroencephalography	1 (1)
Raised creatinine	1 (1)
Hypertension	1 (1)

Table 5 Laboratory investigations

Investigation	*No of cases studied*	*Result*
White cell count (×10⁹/l)*	89	4·4–49·(
Erythrocyte sedimentation rate (mm in first hour)*	73	14–180
Platelet count (×10⁹/l)*	93	110–145
C reactive protein	28	Raised
Antistreptolysin O titre	40	Raised i
Anti-DNAse B titre	27	Raised i
Pyuria	70	Present
Proteinuria	70	Present
Cerebrospinal fluid white cell count	20	Raised i
Plasma albumin (g/l)*	63	20–45
Asparartate aminotransferase (IU/l)*	58	13–990
Alanine aminotransferase (IU/l)*	53	10–638
IgG	33	Raised i
IgA	33	Raised i
IgM	33	Raised i

*Results are range (mean).
†Infected in three; ‡infected in one.

phase response with a rise in their erythr
sedimentation rate, white cell and pl
counts, and C reactive protein concentra
however, none of these responses is specif
the disease. The results are shown in tab

Autoantibodies were measured in 23 c
There was a mildly raised antinuclear anti
in two cases and a slightly raised sn
muscle antibody in five patients. Antineutr
cytosolic antibodies and antiendothelial
antibodies have been measured more recen
patients with Kawasaki disease and have
reported separately,[4 5] but both have
shown to be raised in most patients with K
saki disease in whom they were meas
Microbiological investigations did not sh
consistent infecting organism.

PREDICTION OF CARDIAC SEQUELAE

An attempt was made to see if any of the la
tory variables might predict cardiac inv
ment. The platelet count was signific
higher in the group with cardiac disease
pared with those with no cardiac involve
($p<0·001$). The white cell count was sim
higher ($p<0·01$) in the group with cardiac
ease. There was no significant difference i
erythrocyte sedimentation rate between gro

Treatment

A wide variety of treatment regimes were
changing as the therapeutic policies altered
the 12 year period. The treatment was aim
initially decreasing inflammation and inhib
platelet aggregation and this was achieved
dominantly with aspirin and dipyridar

Eighty nine cases received aspirin and of these 48 did so in combination with dipyridamole. With the advent of Sandoglobulin (Sandoz) in reducing the incidence of coronary artery involvement,[6 7] administration of this agent has become standard practice in recent years. Twenty seven cases were treated with Sandoglobulin usually with either aspirin or aspirin and dipyridamole. In 10 cases with ischaemic cardiac disease and/or giant aneurysms prostacyclin was used as an antiplatelet agent and in some severe cases plasma exchange or exchange transfusion (two cases), heparin (three cases), and streptokinase (one case) were used, in a variety of combinations with other drugs. Antibiotics were administered at some time during the acute phase of the disease in 59 and five cases received no treatment.

Outcome and sequelae

The patients have been followed up for a period of up to seven years with a mean of 1·23 years. One patient died after a myocardial infarction at 10 days. One patient relapsed seven years after his initial episode of Kawasaki disease, which had not been complicated by coronary artery involvement. However on the second episode he had appreciable coronary aneurysms, which have persisted for a year.

Many of the patients demonstrated some of the features of Kawasaki disease at times of recurrent 'viral' infections and some children had recrudescence of symptoms while still in the convalescent phase of their initial disease. In addition, one patient developed cerebellar ataxia and two patients complained of chest pain after resolution of the primary illness but neither was found to have evidence of cardiac involvement. Seventy four cases made what was considered to be a complete recovery with no obvious sequelae.

Cardiovascular sequelae, defined as abnormalities present at one month or later occurred in 27 cases (table 6). One patient died during the first month but apart from this child there was a continuing resolution of the cardiac complications. Of eight cases who had been followed up for 2·5 years only one had persistent aneurysms.

Table 6 Cardiac sequelae present at one month or later (n=27, one case had two sequelae)

	No of cases
Persistent aneurysms	13
Dilatation	10
Left ventricular dyskinesis/left ventricular hypertrophy	2
Pericardial effusion	3

One patient relapsed with the full syndrome and severe cardiac involvement. There were no episodes of Kawasaki disease in siblings concurrently, although one of the patients had a sibling who had had the disease several years before.

Discussion

The patients described in this series have similar characteristics and results of laboratory investigations when compared with other larger series in Japan and the United States.[8 9] The male to female ratio of 1·27:1 was slightly lower than that quoted in the Japanese and American data where the ratio is approximately 1·5:1.[10] The peak age of 0–1 years was similar to the peak age of 9–11 months in Japan.[9] It is known that atypical cases of Kawasaki disease do occur. The data from the BPSU showed the mortality of the children who satisfied three criteria was substantially higher than those who satisfied four, five, or six criteria.[2] We therefore did include a few cases that fell into this category.

There were no major epidemics as have occurred in Japan in 1979, 1982, and 1985–6,[9] and the general increase in the number of cases may in part reflect an increase in the awareness of the disease. Our series showed a tendency to a higher incidence in the spring and early summer in contrast with the more frequent finding of a greater number of cases in the winter and early spring in other reported series.[11]

Kawasaki disease is known to occur in all races with Oriental people being the most often affected, followed by Afro-Caribbeans, with whites proportionately appearing to be protected. This pattern of distribution was reflected in our group of patients.

Our overall incidence of cardiac complications is slightly higher than that normally quoted,[9] but in this study we have included complications such as pericardial effusions, which are not necessarily due to coronary artery disease. Our incidence of aneurysms, however, is not dissimilar to other reports in the literature.[11] For a more detailed description of the cardiac complications in the group of patients seen at this hospital the reader is referred to a second paper dealing specifically with the cardiological aspects.[3] It is clear, however, that the majority of detectable cardiac abnormalities in our population of patients resolved within one to two years. There is debate as to whether these children may be at risk of premature atherosclerosis. There have been reported cases of young adults suffering myocardial infarction who were subsequently found to have coronary artery aneurysms consistent with those found in Kawasaki disease,[12] and in one case a history of a Kawasaki like illness in childhood.[13] The issue of low dose aspirin treatment for a prolonged period remains controversial and the approach to management of this problem is discussed in the second paper but it is clear that these children need to be followed up long term so that this type of question can be answered.

No major conclusions can be drawn from the results of the various treatment regimes utilised at this hospital due to the changes that have occurred over the years. The findings of Furusho *et al*[6] and Newburger *et al*[7] that showed a significant decrease in the incidence of coronary artery disease after the use of immunoglobulin has, however, resulted in this becoming standard treatment for affected children. Due to the hospital's tertiary referral pattern the patients were often started on immunoglobulin treatment rather later in the course of the disease than would have been preferred and this may explain the lack of a striking decrease in the cardiac disease after immunoglobulin treatment. The particular experience in the use of both prostacyclin and exchange transfusion is noteworthy. Prostacyclin is a potent inhibitor of platelet aggregation. In a disease where platelet aggregation is found to occur it may obviously have benefits in preventing the release of vasoactive mediators and thrombotic complications.[14] Prostacyclin's vasodilator properties are also of use in this disease and no adverse effects occurred in any of the patients in whom it was used. Exchange transfusion may have benefits similar to that of plasma exchange in polyarteritis nodosa[15] or other systemic necrotising vasculitides and thus may have a role in the extremely sick infant.

The aetiology of Kawasaki disease remains unknown. A number of organisms have been implicated but none confirmed. In patients in whom comprehensive microbiological investigation was undertaken no consistent findings emerged. The possible role of retroviruses has been extensively investigated by many groups.[16 17] However the initial positive findings have more recently been refuted.[18] We also support this lack of positive data having studied some of our recent patients in collaboration with Professor R Weiss and his colleagues at the Institute of Cancer Research and we found no evidence of retroviral involvement (R Weiss, personal communication).

Although the number of cases of Kawasaki disease seen in the United Kingdom is small compared with other areas of the world, the disease still accounts for significant morbidity in the paediatric population and it remains important to continue follow up to establish the long term outlook for these patients.

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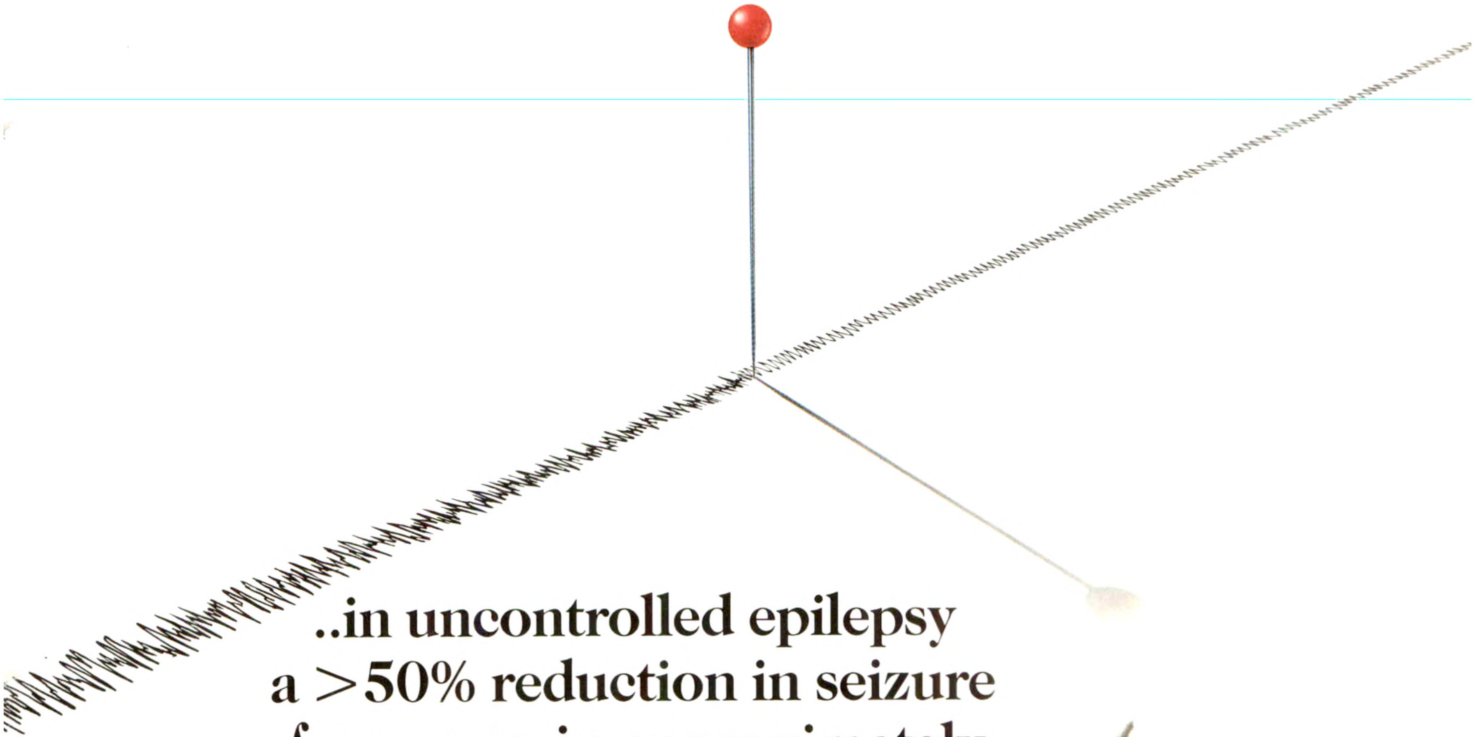

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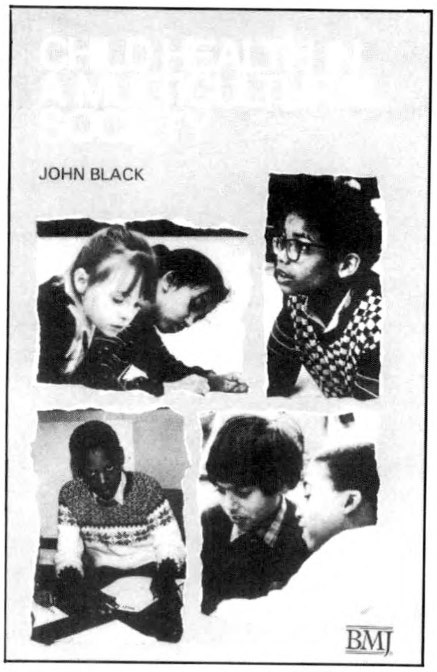

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Antiendothelial cell antibodies detected by a cellular based ELISA in Kawasaki disease

E J Tizard, E Baguley, G R V Hughes, M J Dillon

Abstract

Kawasaki disease is an acute vasculitic illness of childhood associated with significant morbidity and mortality. A cellular based enzyme linked immunosorbent assay (ELISA) was used to demonstrate the presence of antiendothelial cell antibodies in sera from children with Kawasaki disease. Twenty one of 32 patients with Kawasaki disease had raised IgM antibody titres and four had raised IgG antiendothelial antibody titres. There was a significant difference in the IgM antiendothelial cell antibody titres when comparing the patients with normals and febrile controls. The antibody titre paralleled the disease activity in patients studied serially. There was no relative increase in binding of antiendothelial cell antibodies after cytokine stimulation. These findings may be of importance in further research into the understanding of mechanisms involved in this and other forms of vasculitis in man.

Kawasaki disease is a form of acute systemic vasculitis of childhood, which was first described in 1967.[1] Since that time over 80 000 cases have occurred in Japan. Although the disease is less common in the United Kingdom approximately 70–90 cases per year have been reported since the introduction of the active reporting system through the British Paediatric Surveillance Unit in 1986, and this is probably still an underestimate.[2] The disease manifests itself as a febrile illness associated with mucosal inflammation, lymphadenopathy, rashes, and peripheral desquamation. In approximately 20% of cases cardiovascular complications develop secondary to coronary vasculitis. The presence of coronary artery aneurysms may lead to coronary thrombosis, myocardial infarction, and in approximately 1% of cases there may be a fatal outcome.[3]

The aetiology of this disease is still unknown but an infectious agent is suspected. Numerous organisms, including retroviruses, have been implicated but none confirmed.[4] The infectious aetiology theory is supported by the seasonal incidence and the epidemics that have occurred in some countries.[5]

In the absence of a specific laboratory test the diagnosis at present depends on the presence of five out of six of the established clinical criteria providing other illnesses are excluded.[6] There is evidence that immunological mechanisms are activated in Kawasaki disease. In vitro studies have demonstrated an increase in the number of activated lymphocytes spontaneously secreting IgG and IgM, increased activated T helper cells, and a deficiency of circulating suppressor/cytotoxic cells in children with this illness.[7] Recently antibodies cytotoxic to cytokine stimulated endothelial cells have been demonstrated in the acute phase of Kawasaki disease.[8 9]

Using a cellular based enzyme linked immunosorbent assay (ELISA) system[10] we have studied the presence of antiendothelial cell antibodies and their binding to cytokine stimulated endothelial cells in serum from children with Kawasaki disease.

Patients and methods

PATIENTS

Thirty two cases which fulfilled the clinical criteria for Kawasaki disease were evaluated. These included either patients referred to the Hospital for Sick Children or patients presenting at other hospitals with Kawasaki disease whose paediatricians sent serum samples to us. Sera were collected prospectively and in most cases from children as early as possible in the disease and in some cases serial samples were measured. Initial samples range from day 6 to day 51 of the illness and were stored at −70°C before testing.

Two control groups were also studied both of whom needed blood samples for routine clinical purposes. The first consisted of normal children admitted to the Hospitals for Sick Children for routine surgery or those undergoing investigation of short stature, and the second including children admitted with acute febrile illnesses.

The age range of the patients was 0·3–12·6 years (mean 2·34) and included 18 boys and 14 girls. The majority of patients were white with five West Indians and four Japanese. The age range of the febrile controls was 0·66–10·25 years (mean 3·05) and that of the normal controls 1·08–16·7 years (mean 7·41). The control groups were mainly white children.

Coronary artery abnormalities occurred in 15 of the 32 patients. Coronary artery aneurysms were found in 10/32 (31%) and coronary artery dilatation in a further 5/32 (16%).

Approval was obtained from the ethical committee of the Hospitals for Sick Children and the Institute of Child Health for collecting serum samples from patients and controls.

ENDOTHELIAL CELL CULTURE

Human umbilical vein endothelial cells were obtained by collagenase (Sigma) digestion using a modified method as described by Jaffe.[11] Unpooled cells were grown to confluence in 25

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ml flasks (Nunc) precoated with 1% gelatin solution (Sigma) in Roswell Park Memorial Institute (RPMI) medium 1640 with glutamine (Gibco), 20% heat inactivated fetal calf serum (Gibco), and 100 U/ml penicillin and streptomycin (Flow). The cells were incubated at 37°C, 5% carbon dioxide, and fed at three day intervals. When confluent they exhibited a typical cobblestone appearance by phase contrast microscopy and 95% positivity for factor VIII, by immunofluorescence. Cells from individual flasks were transferred to a precoated 96 well gelatin microtitre plate (Nunc) after removal with a 0·2% trypsin EDTA solution (Flow). Cells were plated at 2×10^4 per well at which density they were seen to be confluent by phase contrast microscopy after an overnight incubation. They were used in the ELISA within four days and plates where cell growth was found to be uneven were discarded.

ANTIENDOTHELIAL CELL ELISA

All stages of the ELISA were performed at 37°C in 5% carbon dioxide using medium RPMI 1640 with glutamine, 10% fetal calf serum, and 10% adult bovine serum (Imperial) diluent. The plates were checked for confluence before the start and throughout the ELISA by phase contrast microscopy. Initially 180 µl of diluent was added to block non-specific binding sites. After two washes with sterile phosphate buffered saline, test sera diluted one in 50 were added to five adjacent wells. After a three hour incubation the plate was again gently washed twice with sterile phosphate buffered saline and 120 µl/well of goat antihuman polyvalent, IgG or IgM antibody (Sigma), at a dilution of 1:350, or 1:500 respectively, added to each well. Samples were run in quintuplicate. After a two hour incubation the plates were washed twice with phosphate buffered saline and 75 µl of nitrophenolphosphate substrate in diethanolamine buffer at pH 9·8 added. The reaction was stopped after 90 minutes by the addition of 75 µl/well of 3M sodium hydroxide and the plates were read using a Titertek multiscan with a 405 nm filter.

Initial screening of patients with systemic lupus erythematosus had identified a patient with high binding who was adopted as the positive standard for all experiments. Similarly a normal control sera with relatively low reactivity was selected to be a negative control for all experiments (background levels were assessed using diluent alone).

For each serum tested a binding index ratio was calculated using the following formula (OD, optical density):

$$\frac{\text{(OD test sera}-\text{OD negative standard)}}{\text{(OD positive sample}-\text{OD negative standard)}}\times100$$

Initially 65 blood donors were screened (arithmetic mean (SD) 11 (9)) and results were taken as abnormal if they were greater than 3SD above the mean (40%) for this group. Only one patient was positive at this level. The coefficient of variation between plates was 7·5%.

CYTOKINE PRESTIMULATION

(1) Interferon gamma

Altogether 96 well microtitre plates were prepared as for the ELISA studies and checked for confluence of endothelial cells using phase contrast microscopy. The medium was then aspirated and 200 µl/well of fresh medium added to half of the plate. Finally 200 µl/well of recombinant interferon gamma at a dilution of 100 U/ml was added to the remaining half of the plate. The plate was then incubated for 48 hours before running the ELISA, which was modified to allow identical samples in quintuplicate to be run concurrently in both stimulated and unstimulated halves of the plate. Interferon gamma activity was initially investigated by studying the dose response expression of class I and class II molecules. One aliquot of interferon gamma was divided into separate aliquots at −70°C to be used in all experiments, and therefore was not checked on each occasion.

(2) Tumour necrosis factor

Plates were prepared as for the experiments with interferon gamma, tumour necrosis factor–α (AMGEN) at a dilution of 50 U/ml being substituted for interferon gamma to prestimulate the endothelial cells on half of the plate. Plates were then incubated for 90 minutes before being used in the modified ELISA as detailed above. As with the interferon gamma, tumour necrosis factor was initially aliquoted and frozen until used in individual assays.

Statistical analysis was performed using the Mann-Whitney U test.

Results

Twenty one of the patients with Kawasaki disease demonstrated titres of IgM antiendothelial cell antibodies greater than 40% of the standard positive control. This level was opted for being the mean +3SD of the standard positive control when evaluated on blood donor sera. There was a significant difference between the Kawasaki disease group and the normal controls ($p<0·001$) and also the febrile controls ($p=0·001$) (fig. 1). Four children also showed raised titres of IgG antiendothelial cell antibodies but this was not significant

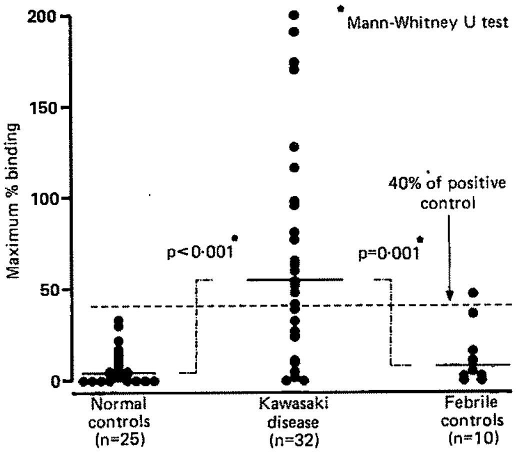

Figure 1 IgM antiendothelial cell antibodies in Kawasaki disease.

(fig 2). Serial measurements of IgM antiendothelial cell antibodies in six patients showed an initial rise in antibody titre with a fall in the convalescent period (fig 3). In one patient IgG antiendothelial cell antibodies were seen to rise as the level of IgM fell (fig 4). In this patient Sandoglobulin (Sandoz) had been given as part of the treatment but the IgG antiendothelial cell antibodies titre continued to rise long after the administration of gammaglobulin.

CYTOKINE STIMULATION EXPERIMENTS

After 24 hours of stimulation of the endothelial cells with recombinant interferon gamma a morphological change in the cells was seen with the endothelial cells becoming elongated. ELISAs using mouse monoclonal antibodies to class I antigens (W6 32) and class II antigens (Royal Free DR) confirmed significant stimulation of the endothelial cells in a dose related response (table 1). Similarly tumour necrosis factor was shown to be effective at 90 minutes incubation.

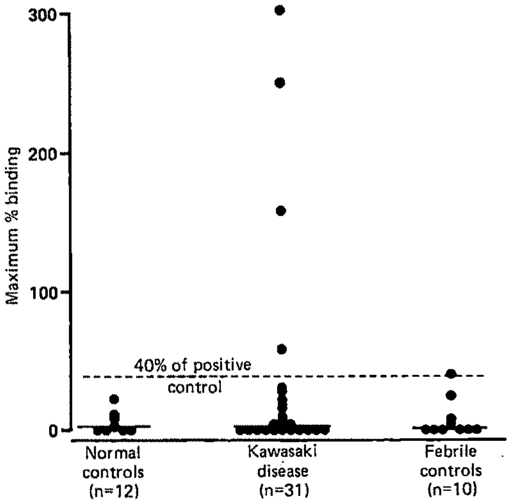

Figure 2 IgG antiendothelial cell antibodies in Kawasaki disease.

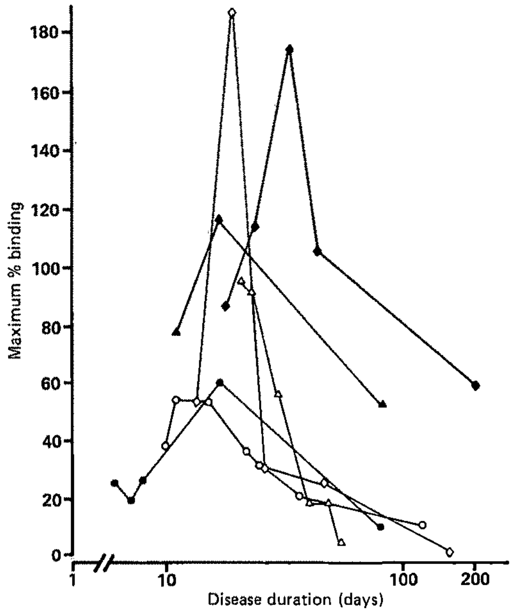

Figure 3 Serial IgM antiendothelial cell antibodies in six patients with Kawasaki disease.

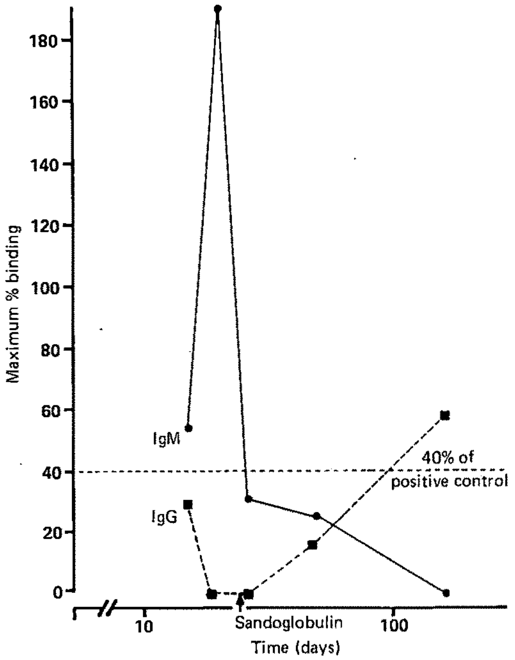

Figure 4 Serial IgG and IgM antiendothelial cell antibodies in one patient with Kawasaki disease.

In 15 patients tested for IgM antiendothelial cell antibodies no enhancement of the binding was seen after prestimulation of the endothelial cells with interferon gamma. There was also no enhancement found in 10 patients tested for IgG antiendothelial cell antibodies. Three of four patients showed increased binding of polyvalent antisera after stimulation of the endothelial cells with interferon gamma. Two of four patients exhibited enhanced binding of IgG antiendothelial cell antibodies after a 90 minute prestimulation of the endothelial cells with tumour necrosis factor. This was not observed in four patients tested for IgM antiendothelial cell antibodies binding after stimulation by tumour necrosis factor (table 2).

Table 1 Expression of class I and II antigens correlated with dose and time of incubation with interferon gamma

Dose interferon gamma (U)	*Optical density (SD)*	
	Royal Free DR (class II)	*W632 (class I)*
Incubation time:		
24 Hours		
0	0·037 (0·101)	0·140 (0·014)
10	0·360 (0·048)	0·380 (0·046)
100	0·323 (0·037)	0·468 (0·062)
48 Hours		
10	0·568 (0·101)	0·389 (0·064)
100	0·773 (0·068)	0·421 (0·075)

Table 2 Effect of cytokine stimulation on binding of antiendothelial cell antibodies in Kawasaki disease

No of patients	*Antibody + cytokine*	*Results*
10	IgG + interferon gamma	No change
15	IgM + interferon gamma	No change
4	Polyvalent antisera + interferon gamma	Binding ↑ in three
4	IgG + tumour necrosis factor	Binding ↑ in two
4	IgM + tumour necrosis factor	No change

CLINICAL ASSOCIATION OF ANTIENDOTHELIAL CELL ANTIBODIES

Of the 15 patients with cardiac sequelae nine had raised titres of IgM antiendothelial cell antibodies. Twelve patients without coronary artery lesions also demonstrated raised titres.

Discussion

Using a cellular based ELISA system we have been able to demonstrate antibodies, predominantly of the IgM class, which bind to the surface of umbilical vein derived human endothelial cells. These antibodies were found in children with Kawasaki disease, but not febrile controls or normals. Serial studies in six positive patients showed an association between the antibody titre and the stage of the disease and this may explain some of the negative results in patients either in whom samples were taken too early to detect antibody production or in whom sampling was delayed.

Previous work has suggested the presence of antiendothelial cell antibodies in Kawasaki disease which are cytotoxic to endothelial cells prestimulated with cytokines, interferon gamma, tumor necrosis factor, and interleukin 1.[8 9] It is of interest that we were unable to demonstrate enhancement of binding after prestimulation of the endothelial cells with interferon gamma and tumour necrosis factor in the majority of samples. This discrepancy may in part be explained by the method of calculating the binding index of the tested sera. In the calculation the binding of the negative sample is subtracted from that of both the positive and test sera. We observed an increase in the antibody binding (that is, optical density) of the samples after cytokine stimulation when compared with the identical samples on the unstimulated cells. Because of an equal increase in both negative and positive sera, however, the net binding observed was unchanged. This enhancement may be sufficient to cause the cytotoxicity seen in the experiments of Leung *et al.*[8 9] Attempts were made to reproduce the cytotoxicity observed by Leung *et al*, albeit by a slightly different technique, but unfortunately complement in the recommended dilution caused cell lysis. Further experiments are needed in this area. We do, however, feel that our results are consistent with those of Leung *et al.*

It might have been hoped that we would be able to demonstrate an association between antiendothelial cell antibodies and serious cardiovascular sequelae. However, Kawasaki disease affects many other arteries and it is also possible that other factors are important such as anatomical variation that predispose certain vessels to be involved. Another reason for the lack of association between antiendothelial cell antibodies and cardiac involvement may be due to the failure to collect samples at the peak of antibody production. The ELISA assay for detecting antiendothelial cell antibodies may, however, be of particular use in identifying children with incomplete Kawasaki disease in whom the awareness of potential cardiac complications may be important.

The exact nature of the antigen against which the antibodies are directed is not yet known. It is possible that they are directed against epitopes on the as yet unidentified infectious agent and cross react with antigenic sites on the endothelial cell, thus leading to endothelial damage in the presence of cytokine stimulation. The identification of this antigen might aid the discovery of the infecting agent or vice versa.

Recently the expression of endothelial cell activation antigens has been demonstrated in skin biopsy specimens of children with Kawasaki disease.[12] After treatment with gammaglobulin, which has been shown to reduce the incidence of coronary artery aneurysms in Kawasaki disease,[13 14] Leung *et al* demonstrated the disappearance of endothelial activation in four of six patients.[12] In the remaining two the persistence of endothelial activation was associated with continuing symptoms. There also appeared to be an association between clinical improvement and reduction in cytokine secretion from peripheral blood mononuclear cells, and persistently high levels were associated with coronary artery abnormalities. Thus although we were able to demonstrate binding of antiendothelial cell antibodies to unstimulated cells, it is likely that cytokines influence the cytotoxic effect of the antiendothelial cell antibodies on the endothelial cells.

Taken in conjunction with the cytotoxicity studies of Leung *et al*[8 9] it appears that these antibodies may have an important role in the pathogenesis of Kawasaki disease. The ELISA method is simpler than the cytotoxic assay, described by Leung *et al*, for determining the presence of these antibodies and although antiendothelial cell antibodies are not specific for Kawasaki disease, they may be a useful tool in understanding the pathophysiology of this and other forms of vasculitis.

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A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features

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Abstract

Twelve infants (six boys, six girls) with severe hypocalcaemic tetany or convulsions were seen over a three year period. Nine patients were symptomatic in the newborn period. Their hypocalcaemia was associated with hyperphosphataemia and very low concentrations of immunoreactive parathyroid hormone. None of the babies suffered from congenital cardiac disease. Cell mediated immunity, measured in five patients, was normal. There were no chromosomal abnormalities but all patients shared several dysmorphic features including deep set eyes, microcephaly, thin lips, beaked nose tip, external ear anomalies, micrognathia, and depressed nasal bridge. Mental retardation of varying degree was found in all patients. All had severe intrauterine and postnatal growth retardation. Four patients have died. The remaining eight patients are on treatment with vitamin D and calcium supplements with no change in their growth pattern. We believe that this association of congenital hypoparathyroidism with severe growth failure and dysmorphism represents a new syndrome.

Hypoparathyroidism represents a range of clinical and biochemical syndromes characterised by parathyroid hormone deficiency, hypocalcaemia, and hyperphosphataemia. Neonatal hypoparathyroidism is relatively common, occurring usually as a transient condition associated with well defined risk factors such as prematurity, perinatal asphyxia, and maternal diabetes.[1] Permanent congenital hypoparathyroidism is rare. Most cases are caused by defective embryogenesis of structures deriving from the third and fourth pharyngeal pouches and fourth branchial arch—namely the parathyroid glands, thymus, heart and aortic arch, and several facial structures. This constellation of findings is known as third-fourth pharyngeal pouch syndrome or DiGeorge's syndrome.[2]

In the past three years we have identified 12 patients with an unusual syndrome of congenital hypoparathyroidism associated with severe growth failure and dysmorphic features quite distinctive from those of DiGeorge's syndrome. The description of their clinical findings and laboratory investigations is the subject of this report which was presented in part at the 58th Annual Meeting of the Society for Pediatric Research, Washington DC, May 1988.[3]

Patients and methods

RECOGNITION OF THE SYNDROME

The index case (case 1) was a 3 year old Saudi boy who was the product of a normal full term pregnancy and spontaneous vaginal delivery. His birth weight was 1500 g. Hypocalcaemic tetany was diagnosed in the first few days of life and was treated with oral calcium supplement and a vitamin D preparation. His parents were first degree cousins and had two older children in perfect health.

He was referred to our care at the age of 4·5 months because of repeated attacks of vomiting and convulsions. His weight was 2·5 kg and length 47 cm. Physical examination disclosed moderate dehydration and several dysmorphic features including microcephaly, micrognathia, thin lips, low set and posteriorly rotated ears, deep set eyes, depressed nasal bridge and beaked nose tip, and high arched palate. Examination of the heart and lungs showed no abnormalities and there was no abdominal visceromegaly. He had small hands and feet, micropenis, and unilateral cryptorchidism. He had normal blood urea nitrogen and creatinine concentrations and moderate hyponatraemia, which was corrected with appropriate treatment. His serum calcium concentration ranged from 1·5 to 1·7 mmol/l, and inorganic phosphate from 2·3 to 4·0 mmol/l. Parathyroid hormone, measured on five occasions, ranged between 10–30 pmol/l (normal 29–85 pmol/l) despite severe concomitant hypocalcaemia.

Two unrelated patients (cases 2 and 3) with similar phenotypic abnormalities had been seen by one of the authors (NAS) in the preceding 12 months. Both were found to have congenital hypoparathyroidism and severe growth failure. In the next two years, nine additional patients from eight unrelated families fulfilled the criteria for inclusion in this report.

LABORATORY METHODS

All patients had serial determinations of serum calcium, phosphate, magnesium, albumin, and creatinine concentrations in addition to routine laboratory studies. Parathyroid hormone was measured by radioimmunoassay against the mid region of the molecule utilising a commercial kit (INCSTAR Corporation). T and B lymphocyte quantitation, performed in five patients, was measured by monoclonal antibody with laser beam sorter. T lymphocyte function was measured by blastogenesis with several mitogens including pokeweed, phytohaemagglutinin, and concanavalin A.

Results

CLINICAL AND LABORATORY FINDINGS

Table 1 summarises the clinical and laboratory data of the 12 patients. Sex distribution was

Table 1 Clinical findings in patients with congenital hypoparathyroidism

Case No	Sex	Gestational age (weeks)	Birth weight (g)	Age		Consanguinity	Family history	Karyotype	Mental retardation	Additional data
				Onset of symptoms	Diagnosis					
1	M	Full term	1500	7 days	4 months	First cousins	Negative	46XY	Moderate	Recurrent vomiting, pylo stenosis, operated
2	F	Full term	3000	25 days	25 days	First cousins	Positive	46XX	Severe	Esotropia, nystagmus, ac auricle
3	M	Full term	1610	30 days	30 days	First cousins	Negative	46XY	Moderate	Death from fulminant pne 5 months of age
4	F	Full term	Low birth weight	3 months	3 months	First cousins	Negative	46XX	Severe	Esotropia
5	M	35	1650	1 day	1 day	First cousins	Negative	46XY	Moderate	Died at 7 months of age, p
6	F	Full term	2100	17 days	25 days	First cousins	Positive	ND	Moderate	
7	F	34	1400	4 months	4 months	First cousins	Positive	ND	Severe	Died at 2 years of age, case 8
8	M	Full term	2150	2 days	12 days	First cousins	Positive	ND	Severe	Sibling of case 7
9	M	32	2100	21 days	7 months	Fourth cousins	Positive	46XY	Severe	Bilateral corneal opacity, d tubular acidosis, died at of age
10	F	30	1600	2 months	15 months	First cousins	Negative	46XX	Moderate	
11	F	36	1750	7 months	9 months	None	Negative	ND	Mild	
12	M	Full term	2000	15 days	2 months	First cousins	Negative	46XY	Mild	Chickenpox at 10 days o

ND, not done.

equal. All but one patient (case 2) suffered from severe intrauterine growth retardation with birth weights ranging from 1500 to 2150 g. Five patients were born prematurely. Ten patients were born of parents who were first degree cousins. Four families had more than one child affected with a similar condition.

The presenting complaint in all patients was hypocalcaemic tetany or generalised convulsions, usually detected in the first few days or weeks of life. In two patients the onset of symptoms was delayed until the fourth and seventh month. Additional manifestations shared by all patients were severe growth failure and psychomotor retardation. Feeding disorders, vomiting, and diarrhoea were other common problems encountered.

The results of the biochemical investigations are listed in table 2. All patients had moderate to severe hypocalcaemia and hyperphosphataemia. The normal serum calcium found in case 11 was the result of treatment with vitamin D before her referral to our care. Three patients had a low serum magnesium concentration. The parathyroid hormone concentration was low in all patients despite concomitant severe hypocalcaemia. In cases 6 to 12 parathyroid hormone was reported as less than 30 pmol/l because this was the limit of detection of the assay. Renal function, judged from serum urea and creatinine concentrations, was normal in all patients.

One patient had an associated distal ren lar acidosis requiring alkali treatment.

All patients had several dysmorphic f these and other findings are summar table 3. The most characteristic were t niofacial findings consisting of microc deep set eyes, thin lips, micrognath pressed nasal bridge with beaking of tl

Table 3 Dysmorphic features and other clinical f 12 patients with congenital hypoparathyroidism a growth failure

Abnormal:	
Microcephaly	12
Deep set eyes	12
Thin lips	12
Beaked nose tip	10
Low set and/or posteriorly rotated ears	10
Micrognathia	10
Prominent forehead	10
Depressed nasal bridge	10
Small hands and feet	10
Microphthalmos	6
Esotropia	5
Micropenis	4
Cryptorchidism	2
Nystagmus	3
Epicanthic folds	2
Normal:	
Cardiovascular system	12
Absence of visceromegaly	12
Growth hormone	8
Thyroid function	7
T lymphocytes	5
Immunoglobulins	5

Table 2 Results of biochemical analysis of serum in patients with congenital hypoparathyroidism

Case No	Calcium (mmol/l)	Phosphate (mmol/l)	Magnesium (mmol/l)	Alkaline phosphatase (IU/l)	Parathyroid hormone (pmol/l)	Albumin (g/l)	(
1	1·4	2·7	1·1	188	25	38	2
2	1·6	3·4	0·8	238	20·5	37	3
3	1·5	3·3	0·8	88	19	38	2
4	1·2	3·3	1·2	228	17	35	2
5	1·3	4·1	0·8	28	9·1	40	4
6	1·8	4·7	0·8	118	<30	42	4
7	1·75	3·2	0·8	18	<30	44	5
8	1·67	3·5	0·55	300	<30	41	4
9	1·35	3·2	0·6	216	<30	39	6
10	1·8	2·44	0·8	174	<30	42	4
11	2·29	2·45	0·8	260	<30	42	3
12	1·3	3·2	0·5	150	<30	40	3
Normal values	2·1–2·6	1·2–1·95	0·75–1·0	100–300	30–85	37–47	3

Table 4 Follow up growth data in patients with congenital hypoparathyroidism

Case No	*Birth weight (g)*	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Weight (SD score)*	*Height (SD score)*
1	1500	3·5	5·4	69·0	−5·8	−7·1
2	3000	5·5	6·4	76·0	−5·2	−7·2
4	Low birth weight	3·8	7·5	75·0	−5·4	−5·9
5	2100	1·3	4·8	59·0	−5·5	−7·6
7	1400	2·0	2·0	44·5	−7·6	−12·5
8	2150	1·0	4·0	52·5	−5·3	−9·0

[redacted]

and depressed nasal bridge were also very common abnormalities.

Several patients in the series were referred from other hospitals to exclude the diagnosis of DiGeorge's syndrome, which is also characterised by congenital hypoparathyroidism and facial dysmorphism. There are several differences between patients with DiGeorge's syndrome and those we have described. First, in DiGeorge's syndrome there is aplasia or hypoplasia of structures deriving from the third and fourth pharyngeal pouches leading to thymic aplasia and cellular immunodeficiency as well as hypoparathyroidism.[2 5] None of our patients showed clinical evidence of T cell deficiency such as chronic monilial infections, diarrhoea, rhinitis, or skin rashes. Intact cell mediated immunity was demonstrated in all five of the patients tested at various ages who had a normal T lymphocyte blastogenic response to a variety of mitogens. Second, most patients with DiGeorge's syndrome have significant congenital cardiac anomalies including conotruncal defects and aortic arch malformations.[5] Cardiovascular abnormalities were not seen in any of our cases. Third, the facial dysmorphism of DiGeorge's syndrome is quite unlike that of our patients. Commonly described features include hypertelorism, abnormal and pointed ears, anteverted nostrils, micrognathia, and antimongoloid slant. Of these, only micrognathia and possible ear anomalies were comparable with our cases. Lastly, the severe intrauterine growth retardation observed in 11 of 12 patients in our series is not a feature described in DiGeorge's syndrome.[2]

Congenital hypoparathyroidism has been reported in association with a variety of developmental anomalies, including lymphoedema, nephropathy, nerve deafness, congenital heart disease,[5–8] and chromosomal abnormalities.[9–11] Some of the reported cases may represent incomplete forms or variants of the third to fourth pharyngeal pouch syndrome of DiGeorge. More recently, congenital hypoparathyroidism has been reported in association with the Silver-Russell syndrome[12] and the Kenny syndrome of dwarfism, internal cortical thickening, and medullary stenosis of tubular bones.[13]

The pathophysiology of hypoparathyroidism in our patients and its association with the multiple abnormalities described remain elusive to us. With the available data, it is impossible to tell whether the parathyroid glands were absent or hypoplastic or whether they were present but not adequately producing or releasing parathyroid hormone into the circulation.

The mode of inheritance in this syndrome is most probably autosomal recessive. This is suggested by the equal occurrence in both sexes, the familial incidence, and the very high frequency of consanguinity. Of interest is the fact that seven of 12 families came from the western province of the country. It is conceivable that the mutant gene for this disease may have originated from that area. We hope that this report will stimulate the recognition of the syndrome in other families and elsewhere. If, as seems probable, there is a high gene dose for the syndrome in the Kingdom of Saudi Arabia, collaboration between the paediatricians involved will improve the chance of identifying the genotype. As parathyroid hormone deficiency in some cases of familial hypoparathyroidism has been shown to be unrelated to the structural gene for parathyroid hormone,[14 15] the same may apply to the syndrome we have described.

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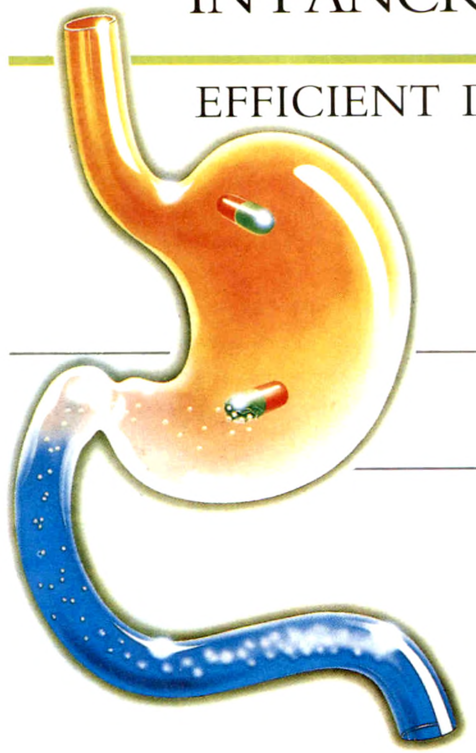

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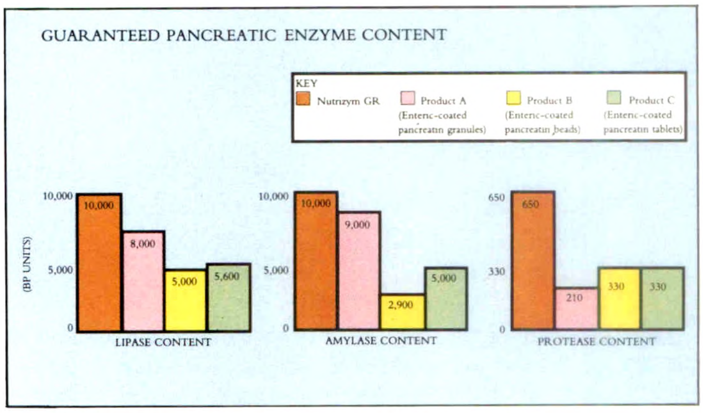

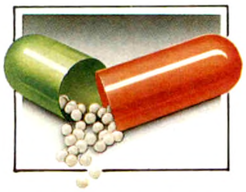

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Archives of Disease in Childhood 1991; **66:** 197–199

Depot testosterone in boys with anorchia or gonadotrophin deficiency: effect on growth rate and adult height

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Abstract

Eleven teenage boys with bilateral anorchia and 12 with gonadotrophin deficiency were treated by injections of testosterone ester (enanthate) at an initial dose of 100 mg every six to eight weeks, rising to 250 mg every four weeks after three to four years. In the anorchic boys average adult height was 177·1 cm, compared with a mean mid-parental height of 174·4 cm, and mean predicted adult heights of 177·0 cm (Tanner-Whitehouse method) and 178·0 cm (Bayley-Pinneau method). In the patients with gonadotrophin deficiency, mean adult height was 176·9 cm, compared with a mean mid-parental height of 176·1 cm, and mean predicted adults heights of 174·0 cm (Tanner-Whitehouse method) and 177·3 cm (Bayley-Pinneau method). We conclude that this testosterone regimen allows achievement of full growth potential in such patients.

During the last 20 years treatment with depot testosterone by intramuscular injection has become well established in the management of boys with different disorders of puberty. Initially introduced for the management of anorchia,[1 2] testosterone has been widely used in the management of constitutional delay of puberty,[3–5] and gonadotrophin deficiency either as an isolated defect or as part of a wider range of anterior pituitary failure.[2 5 6] Though early reports suggested that testosterone treatment might be associated with some reduction in adult height because of rapid advancement in bone age,[7] it is now believed that treatment with low doses of testosterone has no ill effect on ultimate height. Most of the studies supporting this view, however, have been in patients receiving relatively short term courses of testosterone.

The present retrospective study on the effects of testosterone on boys with anorchia or gonadotrophin deficiency was carried out to confirm that the testosterone regimen that had been used had no significant ill effects on adult height. The study also provided an opportunity to compare two different methods of assessing bone age and predicting adult height.

Patients and methods

PATIENTS

The case notes and radiographs of the hands of 11 boys with anorchia (but otherwise normal genitalia), and 12 with gonadotrophin deficiency, 10 of whom also had hyposmia (Kallman's syndrome), were reviewed. They had all received long term treatment with depot testosterone by injection to achieve full masculinistion. Parental heights were known in all the cases.

Surgical exploration had been carried out in 10 of those with anorchia, and the absence of testicular tissue in the remaining case was confirmed by the lack of response to three daily injections of human gonadotrophic hormone (1000 IU). In all these cases basal testosterone concentration was below 1·5 nmol/l before treatment; concentrations of follicle stimulating hormone and luteinising hormone were above 30 IU/l and above 10 IU/l, respectively.

Six of the patients with gonadotrophin deficiency had had orchidopexies for bilateral cryptorchidism. In all these patients basal concentrations of luteinising hormone and follicle stimulating hormone were below 2·6 IU/l, and that of testosterone was less than 1·2 nmol/l before treatment.

After an initial period of observation, depot testosterone (testosterone enanthate) was started at a mean age of 13·2 years (range 11·0–16·0) in the boys with anorchia and 15·1 years (range 12·0–19·7) in those with gonadotrophin deficiency. The difference in the age at start of treatment was the result of later referral of some of the patients with gonadotrophin deficiency, some of whom had previously been thought to have constitutional delay of puberty. Adult heights were obtained for all the patients either from the casenotes (less than 1 cm growth in six months) or by recalling the patient for measurement. Details of the mean ages and heights at the start of treatment and when growth was complete in the two groups of patients are summarised in table 1.

Treatment was usually started with an initial dose of 100 mg testosterone enanthate every six to eight weeks; after one to two years the dose

Table 1 Mean (range) height and weight before treatment and age at start of treatment, in 11 boys with anorchia and 12 with gonadotrophin deficiency, together with mean height, weight, and age when last measured

	Boys with anorchia (n=11)	*Boys with gonadotrophin deficiency (n=12)*
Age at start of treatment (years)	13·2 (11·0–16·0)	15·1 (12·0–19·7)
Height at start of treatment (cm)	152·7 (131·9–169·4)	157·6 (144·2–169·5)
Weight at start of treatment (kg)	42·6 (24·6–58·5)	51·2 (38·5–64·4)
Age when last measured (years)	20·4 (16·2–26·7)	21·4 (17·9–29·7)
Height when last measured (cm)	177·0 (167·2–188·6)	177·8 (165·9–188·1)
Weight when last measured (kg)	64·1 (43·0–78·1)	77·2 (59·2–104·1)

Table 2 Mean growth velocity and weight velocity in 11 boys with anorchia and 12 with gonadotrophin deficiency before starting testosterone and during the first three years of treatment. The mean dose of testosterone for each period is also shown

	Before treatment	*First years' treatment*	*Second years' treatment*	*Third years' treatment*
Anorchia (n=11):				
Mean growth velocity (cm/year)	5·4	8·2	6·9	6·4
Mean weight gain (kg/year)	3·0	7·2	6·6	5·9
Mean body mass index	18·1	19·1	19·7	20·3
Mean dose of testosterone (mg/m^2/month)	Not applicable	51·1	66·7	76·1
Gonadotrophin deficiency (n=12):				
Mean growth velocity (cm/year)	4·8	7·1	5·9	5·8
Mean weight gain (kg/year)	5·0	6·3	5·5	5·6
Mean body mass index	20·6	21·2	22·6	23·0
Mean dose of testosterone (mg/m^2/month)	Not applicable	50·5	73·3	85·5

was increased to 100 mg every four weeks, and after another one to two years it was increased further to 250 mg testosterone ester every four weeks. For the purpose of this study the dose of testosterone has been expressed in mg/m^2 surface area. Mean doses for the first, second, and third years of treatment are given in table 2.

METHODS

Radiographs of the left hand and wrist were available for all the patients before treatment, and they were all scored by BM and MP working together using the Tanner *et al* RUS (radius, ulna, and short bones) method.[8] To assess the reproducibility of the method, the films were then reassessed by BM and MP without knowledge of the patient or the diagnosis, and the results compared. The radiographs were also assessed without knowledge of the diagnosis by DGS using the Greulich and Pyle atlas and the results compared with the initial Greulich and Pyle rating that had been carried out when the patient was first seen.[9]

Predictions of adult height were calculated from the RUS bone scores allocated before treatment by the method of Tanner-Whitehouse,[10] together with the scores derived from the initial Greulich and Pyle rating[9] and those derived from the Bayley and Pinneau tables.[11]

Results

The mean growth velocities of all the patients before treatment are shown in table 2, which also gives the mean growth velocities during the first three years of treatment, mean weight velocities, and body mass index.

In the anorchic boys, mean growth velocity during the first year of treatment increased from 5·4 cm/year to 8·2 cm/year and then fell to 6·9 cm/year and 6·4 cm/year during the second and third years of treatment, respectively. Weight gain increased from 3·0 kg/year to 7·2 kg/year during the first year of treatment, and then fell to 6·6 kg/year and 5·9 kg/year over the next two years, respectively. Body mass index (weight/height m^2) rose from 18·1 to 20·3 after three years of treatment.

Table 3 Mean adult height (cm), mid-parental height, and predicted height at start of treatment calculated by Tanner-Whitehouse and Bayley-Pinneau methods in 11 patients with anorchia and 12 patients with gonadotrophin deficiency

	Anorchia (n=11)	*Gonadotrophin deficiency (n=12)*
Adult height	177·1	176·9
Mid-parental height	174·4	176·1
Predicted height:		
Tanner-Whitehouse	177·0	174·0
Bayley-Pinneau	178·1	177·3

In the boys with gonadotrophin deficiency, mean growth velocity increased from 4·8 cm/year to 7·1 cm/year during the first year of treatment, and then fell to 5·9 cm/year and 5·8 cm/year over the next two years, respectively. Weight gain increased from 5·0 kg/year to 6·8 kg/year, and then fell to 5·5 kg/year and 5·6 kg/year over the next two years, respectively. Body mass index increased from 20·6 to 23·0 during the first three years of treatment.

The adult statures achieved by the two groups of patients are compared with mid-parental height and predicted adult height using the Tanner-Whitehouse and Bayley-Pinneau methods (table 3). Mean adult height (177·1 cm) for the patients with anorchia was slightly less than mean predicted height using the Bayley-Pinneau method (178·1 cm) and almost exactly the same as the mean height obtained by the method of Tanner-Whitehouse (177·0 cm). Mean adult height in these patients was 2·6 cm above mean mid-parental height.

In the patients with gonadotrophin deficiency the mean adult height was 176·9 cm, compared with a mean mid-parental height of 176·1 cm. the mean predicted height using the Bailey and Pinneau method was 177·3 cm and using the method of Tanner-Whitehouse was 174·0 cm, 2·9 cm less than the height attained.

Discussion

Testosterone treatment is well established in the management of delayed or absent male puberty. In an early paper, Aynsley-Green *et al* described the beneficial effect of treatment in a group of boys with anorchia.[1] Since then there have been many accounts of its use in boys with constitutional delay of puberty[3–5] and in chronic medical disorders which are associated with delayed puberty, such as cystic fibrosis.[12] In addition, short term treatment with testosterone has been recommended for differentiating between constituional delay in puberty or gonadotrophin deficiency and growth hormone insufficiency.[13] Treatment with testosterone is also the main method of inducing secondary sexual development in boys with hypopituitarism that is causing growth hormone deficiency associated with gonadotrophin deficiency.[2]

Our results provide further evidence for the safety and efficacy of testosterone ester given by intramuscular injection to produce virilisation in boys with hypogonadism. The regimen that was used produced progressive development of the genitalia similar to that seen in normal male puberty, and in all cases development of the penis and scrotum was judged to be satisfactory after three to four years of treatment. The testosterone regimen does not completely mimic the normal changes of puberty, however, particularly with respect to the timing of peak height velocity. In normal puberty peak height velocity is reached about 18–24 months after the onset of puberty, at a time when testicular development is already well established. In this study, and in the study described by Aynsley-Green *et al*,[1] the most rapid growth occurred during the first year of treatment, and over the next two years growth velocity declined. These findings suggest that the initial dose of testosterone used in both studies may have been too high, and it might be more physiological to use a smaller dose of depot testosterone during the early stages of androgen replacement. Despite this difference in the timing of peak height velocity, however, the regimen described seems to be associated with realisation of full growth potential, judged from both mid-parental heights and adult height predictions based on two different methods.

In our study many of the subjects did not begin treatment until well after the normal age at which puberty begins. This was at least partly related to the late referral of some patients, particularly those with gonadotrophin deficiency who had initially been considered to have straightforward constitutional delay of puberty. We emphasise that such a delay in initiating treatment is inappropriate in most cases, and that the aim of treatment should be to try to mimic the timing of normal puberty as closely as possible, probably by using a lower starting dose of testosterone than that used in our patients.

The effect of testosterone on body habitus and muscle mass is well known, and in our patients this was probably reflected in the increased body mass index that was seen with continued treatment. This increase in both anorchic and hypogonadotrophic patients was similar during a three year period. The initial body mass index was, however, higher in the hypogonadotrophic patients. We do not know whether this is a consistent feature of gonadotrophin deficiency or whether the finding could be related to the relatively advanced age at which some of the patients started treatment.

Our results also provide some information on the use of the Tanner-Whitehouse and Bayley-Pinneau methods of predicting adult height in hypogonadal boys. Zachman *et al* found the method of Tanner-Whitehouse superior to the Bayley-Pinneau method in normal children and in children with familial tall stature, whereas it overestimated adult height in various types of short stature.[14] Similar observations were made by Lenko in normal Finnish children and children with growth delay.[15] In our patients with anorchia the two methods gave similar height predictions, but the method of Tanner-Whitehouse underpredicted mean adult height in the boys with gonadotrophin deficiency.

In summary, our findings provide further evidence of the safety of testosterone replacement treatment in male hypogonadism but we suggest that an initial dose of 100 mg every six to eight weeks may result in rather rapid growth. A lower dose of testosterone might be more appropriate in cases in which treatment is started at the age of 11 to 12 years.

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Correlation of serum antigen and antibody concentration with clinical features in HIV infection

Maadhava Ellaurie, Arye Rubinstein

Abstract

Serum antigen and antibody values were studied in 164 infants and children infected perinatally with HIV. HIV antigens p17, p24, gp41, and gp120 were determined in sera by immunoblot and antigen capture assays. Lymphocyte blast transformation, serum immunoglobulins, and circulating immune complexes were also evaluated. Altogether 50 patients had HIV antigens measured: 31 (62%) patients had p17 antigen in the serum and 29 (58%) had p24 antigen present. In 19 (38%) and nine (18%) patients, respectively, gp120 and gp41 were detected. All four HIV antigens were detected in seven (14%) patients. There was a positive correlation between the concentration of each HIV antigen and clinical outcome. When sequential specimens were analysed, 120 (73%) patients had p24 antigen present.

Patients with stage P2B and P2D (Centers for Disease Control classification) had the highest concentrations of p24 antigen with a mean of approximately 200 pg/ml. Altogether 70% of patients with a p24 antigen concentration of >30 pg/ml eventually died or had severe clinical disease within six to 24 months. Infants under 15 months of age with a p24 antigen concentration as low as 5 pg/ml also did poorly. Increased immunoglobulins and decreases in mitogenic responses and absolute CD4+ lymphocyte counts were more prevalent in patients with raised p24 antigen. Raised concentrations of circulating immune complexes were seen in the symptomatic phase of the disease whereas in the terminal stage of the disease raised serum antigen and a decrease in circulating immune complexes and absolute CD4+ lymphocyte count were evident. Loss of p24 and/or p17 antibody as well as a decreasing ELISA optical density for HIV antibody also signalled progression of the disease.

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HIV is associated with clinical and immunological abnormalities.[1–3] Previous studies in adults indicated that HIV antigenaemia was associated with progressive clinical disease.[4–10] Asymptomatic adults with persistent HIV antigenaemia are at increased risk of developing AIDS or AIDS related complex.[11] In the first few months of life the presence of HIV antigen is thought to be indicative of active disease as HIV antibody could be acquired passively from the mother.[12] In addition, raised and persistent serum antigen concentrations occur in a subset of children with symptomatic HIV infection who do poorly (M Ellaurie *et al*, abstract presented at V International Conference on AIDS, Montreal, 1989).[13–16]

In the present study, we correlated HIV core and envelope antigenaemia with clinical and immunological abnormalities in a large cohort of HIV infected children.

Patients and methods

PATIENTS

One hundred and sixty two perinatally infected infants and children were studied at all stages of HIV infection classified according to the Centres for Disease Control (CDC), Atlanta, Georgia.[17] Two additional patients were infected by transfusion of blood products. The ages of studied children ranged from 1 month to 11 years. The duration of follow up was six months to six years. Sequential determinations of serum antigen concentrations were obtained. In all patients HIV infection was confirmed by repeated serological tests, p24 antigenaemia, viral cultures and/or characteristic clinical symptoms.

Informed consent was obtained from the parents or guardians of the children studied. Human experimentation guidelines of the Albert Einstein College of Medicine were followed in the conduct of the clinical research.

LABORATORY TESTS

Serum immunoglobulins were determined by radial immunodiffusion (RID) using commercially available RID plates (Kallestad Labs).

Immunoblot assay for p17, gp41, and gp120 was done with nitrocellulose paper circles, 1 cm in diameter, that were washed in TRIS (trometamol) buffered saline (TBS), pH 7·5, dried, and placed individually into a 24 well culture plate (Gibco). Sera were absorbed onto the paper circles in two consecutive 2 μl additions and allowed to dry. Unreacted sites on the paper circles were blocked with 3% gelatin in TBS followed by washing with TBS containing 0·05% Tween 20. Mouse monoclonal antibodies against p17, gp41, and gp120 (DuPont Industries), diluted 1:5000 in TBS-1% gelatin, were reacted overnight with dot blots in 250 μl aliquots. After washing with TBS containing 0·05% Tween 20, goat antimouse IgG conjugated to horseradish peroxidase (Biorad Labs) at 1:2500–1:5000 dilution was added. After two hours incubation, 1-chloronaphthol containing hydrogen peroxide was added. The colour reaction was read within half an hour and scored from negative to 4+according to colour intensity.

HIV p24 antigen was measured by a commercially available solid phase antigen capture enzyme linked immunosorbent assay (ELISA) (DuPont). A total of 250 serum samples from 164 patients were evaluated.

Mononuclear leucocytes were isolated from heparinised whole peripheral blood by sedimentation over Ficoll-Hypaque. Blast transformation of patients' lymphocytes was quantitated after stimulation with concanavalin A, pokeweek mitogen, phytahaemagglutinin, and staphylococcus strain Cowan A as previously reported. CD4+ and CD8+ cells were quantitated by flow cytometry using an EPICS-C fluorescence activated cell sorter (Coulter Electronics) as previously reported.

HIV antibody was measured by a commercial ELISA and confirmed by western blot (Epitope).

CIQ assay for immune complexes—circulating immune complexes were measured by a commericial micro-ELISA procedure (Diamedix). Diluted serum specimens were added to goat CIQ coated wells. After incubation, the wells were washed and alkaline phosphatase conjugated antihuman IgG was added. After further washing the substrate p-nitrophenyl phosphate was added. The absorbance was read at 405 nm and results expressed as µg Eq/ml. Normal values were <20 µg Eq/ml.

Statistical analysis was performed by the Student's *t* test.

Results

Fifty patients were evaluated by the immunoblot and antigen capture assays for the presence of the following HIV antigens: p17, p24, gp41, and gp120 (table 1). Thirty one of the 50 patients (62%) demonstrated the presence of p17 antigen in the serum and 29 (58%) had p24 antigen detectable. In nine (18%) gp41 was detected in the serum and gp120 was found in 19 (38%). All four proteins (p17, p24, gp41, and gp120) were detected in seven of the 50 patients (14%).

Table 1 Serum antigen and antibody values in 50 children infected with HIV

	p17	*p24*	*gp41*	*gp120*
No (%) of patients positive for antigen	31 (62)	29 (58)	9 (18)	19 (38)
No (%) of patients positive for antibody	30 (60)	46 (92)	50 (100)	17 (34)
No (%) of patients positive for antigen and antibody	19 (38)	26 (52)	9 (18)	8 (16)

Table 2 Antigens measured by immunoblotting in 50 patients

HIV antigen	*No (%) positive*
p17	31 (62)
p24	29 (58)
gp41	9 (18)
gp120	19 (38)
p17+p24	34 (68)
gp41+gp120	20 (40)
p17 or p24+gp41 or gp120	36 (72)
p17+p24+gp41+gp120	7 (14)

Three patients who were p24 antigen negative were p17 positive by immunoblotting. Thirty four of 50 patients (68%) were p17 and p24 antigen positive and 36 (72%) had at least one antigen present in their sera (table 2).

Utilising the antigen capture assay, p24 antigenaemia was detected in 120 of 164 patients (73%) when sequential specimens were analysed.

In 60% of patients, p17 antibody was detected and p24 antibody was found in 92% of patients. All patients initially had the gp41 antibody and gp120 was found in 34% of patients.

Ninety per cent of all patients were hypergammaglobulinaemic and 82% had decreased mitogenic responses. The absolute CD4+ lymphocyte count was $<600/\times 10^6$ in 50% of patients. Circulating immune complexes were raised in 42 of 60 (70%) patients with a mean (SD) of 62 (70) µg Eq/ml. Patients with detectable serum antigen concentrations had higher serum immunoglobulin concentration compared with patients without detectable antigen (table 3). Decreases in mitogenic responses and absolute CD4+ lymphocyte counts were more prominent in patients with high serum antigen concentrations.

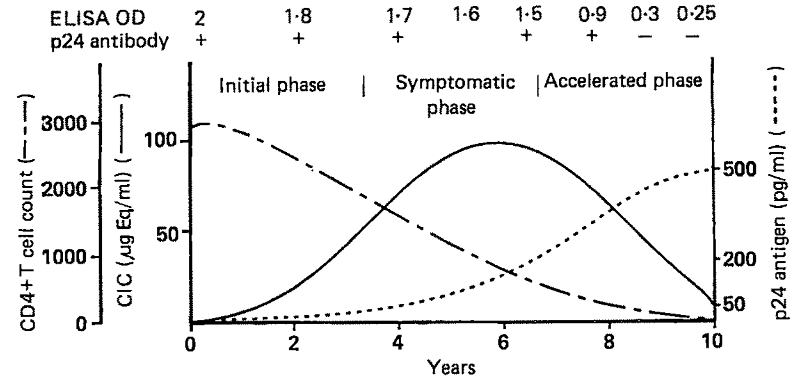
Three distinct phases of HIV infection were noted (figure). In the initial phase concentrations of circulating immune complexes were low and p24 antigen was undetectable or in low concentration. This phase was seen in most patients with CDC stage P2A. In the second or symptomatic phase concentrations of circulating immune complexes were high, p24 antigen was detectable, and the patients were symptomatic. Most of the patients in CDC stage P2B and P2C fell into this category. In the accelerated phase of the disease, the ELISA for HIV antibody frequently became negative, there was a loss of p24 antibody, and circulating immune complexes and CD4+ lymphocyte concentrations became very low and HIV antigenaemia increased before death. Not all patients go through all three phases. The accelerated phase usually followed the initial and symptomatic phases but could be seen in isolation under 1 year of age when patients developed opportunistic infection like *Pneumocystis carinii* pneumonia and died. In the latter case, raised HIV antigen and low circulating immune complex concentrations were observed.

The presence of HIV antigen in the serum preceded other immunological abnormalities

Table 3 Correlation of serum p24 antigen with immunoglobulins, mitogenic responses, and absolute CD4+ lymphocyte count

	IgG	*IgA*	*IgM*	*Depressed mitogenic responses*	*Absolute CD4+ lymphocyte count*
Serum antigen positive (n=21)	2480 (740)	166 (220)	306 (520)	7/21 (33%)	1816 (1046)
Serum antigen negative (n=29)	3306 (380)	433 (383)	665 (540)	15/29 (52%)	326 (206)
p Value	<0·05	<0·05	<0·05	>0·05	<0·05

Results are mean (SD).



Circulating immune complexes (CIC) in µg Eq/ml, HIV p24 antigen in pg/ml, absolute CD4+ lymphocytes, ELISA optical density (OD), and HIV p24 antibody are depicted for one patient. Three phases of the illness are apparent: initial phase with minimal or no symptoms and low CIC, low p24 antigen, and high CD4+ T cells and ELISA OD; symptomatic phase with increased concentration of CIC, a rise of p24 antigen, and a decrease in CD4+ T cells; and accelarated phase with a further rise in p24 antigen and decreased CIC, CD4+ T cells, ELISA OD and loss of p24 antibody before death.

like reversed T4:T8 ratio, hypergammaglobulinaemia, and depression of mitogenic responses in 20 patients and these patients had a poor outcome.

Thirty two of 42 patients (76%) had detectable antigen under the age of 15 months. Twenty of these 32 patients died, 10 had progressive disease, and two had mild symptoms. Patients without or with low serum HIV antigens (1+) had mild symptoms and were clinically stable for 24 months. Patients with high HIV antigen concentration (all four proteins >2+) had more severe clinical disease. The HIV antigen concentrations also increased significantly for months after the development of opportunistic infection. In six patients, viral infections like herpes and varicella also increased HIV p24 antigen with a decrease noted after the acute phase of the infection.

All patients who had greater than 3+ HIV antigen concentration (all four proteins) had opportunistic infection, severe bacterial and viral infection, lymphoma, thrombocytopenia, and chronic pneumonitis. Ninety per cent of these patients died within six to 24 months.

In table 4, the serum p24 antigen is correlated with clinical staging according to the CDC. Thirty per cent of patients in the P2C category had a p24 antigen concentration >100 pg/ml and did poorly. Patients in P2B and P2D stage had the highest mean (SD) concentrations of p24 antigen, 202 (106) pg/ml and 204 (224) pg/ml, respectively. Tests for p24 antigen were more frequently positive in stages P2B, C, D, and E than in stages P2A or P2F.

Persistent antigenaemia was seen in 42 patients and 15 patients had intermittent antigenaemia. Patients with intermittent antigenaemia had a milder disease course, but most of those with persistent antigenaemia had a poor outcome. Only three patients with progressive disease did not have detectable serum antigen. Seventy per cent of patients with p24 antigen concentrations of >30 pg/ml eventually died or had severe disease within six to 12 months. Ten infants under 15 months with a p24 antigen concentration as low as 5 pg/ml did poorly.

Table 4 Correlation of serum p24 antigen with disease stage according to CDC classification

CDC stage	*No of patients*	*p24 Antigen (pg/ml)**	*Log p24 antigen (pg/ml)**
P2A	40	10·9 (2·09)	·58 (0·098)
P2B	20	202 (23·7)	2·25 (0·060)
P2C	35	71·2 (16·9)	1·42 (0·115)
P2D	44	204 (30·8)	2·00 (0·087)
P2E	5	27 (4·4)	1·40 (0·063)
P2F	20	32 (5·1)	1·16 (0·161)

p Value was <0·01 for P2B, C, D, and E *v* P2A; p value was <0·001 for P2C *v* P2B+P2D.
*Values are expressed as mean (SEM).

Twenty of 50 patients (40%) had loss of p24 and or p17 antibody and all these patients had progressive disease. Conversion from ELISA positive for HIV to ELISA negative and/or a decreasing ELISA optical density was seen in 15 patients and this signalled a progressive disease course.

Discussion

HIV antigenaemia has been previously associated with symptomatic disease.[4–10] Severe clinical manifestations were found to be closely related to raised concentrations of HIV p24 antigen in adults. Adults with symptomatic HIV infection had p24 antigen detected more frequently in the serum than asymptomatic adults.

In the present study we evaluated the presence of four HIV gene products in the serum of HIV infected children. The most common gene product was p17 in 62% of patients, followed by p24 (58%), gp120 (38%), and gp41 (18%). Three patients who were p24 antigen negative were p17 antigen positive. Using multiple antigens, the positive yield increased from 58% with p24 antigen alone to 72% utilising all four antigens. Thus an assay system detecting multiple antigens is potentially more useful than detecting p24 antigen alone. We also quantitated the HIV antigens by immunoblot and antigen capture assays and correlated them with disease course. The antibody profile of these patients was also examined.

By studying circulating immune complexes, CD4+ lymphocytes, HIV antigens, and HIV antibody by ELISA and western blot, three stages of HIV disease are apparent. They consist of an initial phase of absent or mild symptoms, a phase with symptoms, and an accelerated phase that precedes death. The results of laboratory tests depend on the stage at which the disease is studied.

In children in whom high concentrations of one or more HIV antigens were detectable in the serum, death followed within six to 24 months and was preceded by increasing HIV antigen concentration. Children who had low or undetectable serum HIV antigen remained stable or had mild symptoms (P2A). Seventy per cent of patients with a p24 antigen concentration >30 pg/ml had a poor outcome. This is in contrast to a previous report in which higher concentrations of p24 antigen denoted a poor prognosis.[15] This may be due to the greater sensitivity of the DuPont antigen capture assay. The reason why 30% of patients with p24 antigen concentrations >30 pg/ml did not do poorly could be due to upregulation of HIV gene expression by infection[18] and tumour necrosis factor.[19] A decreasing antibody concentration as determined by ELISA or loss of p24 and p17 antibody was also indicative of progressive disease as seen in adults.[20] Thus monitoring of HIV antigen and antibody as well as concentrations of circulating immune complexes and CD4+ lymphocytes is of predictive value. Very high p24 antigen concentrations in isolation may not necessarily be predictive of a poor outcome as high values may be seen in association with other viral infections. Therefore, HIV infected children with a p24 antigen concentration >30 pg/ml and poor immune function need to be monitored more closely and treated aggressively. Infants under 1 year with any detectable antigen should also be treated aggressively and given prophylaxis for *P carinii* pneumonia. Other HIV antigens—p17, gp41, and gp120—in addition to p24 are of independent predictive value.

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Shigella seizures

Authors should get their title right if nothing else. My eyes were drawn to a paper headed 'Recurrent seizures in children with Shigella-associated convulsions (Lahat *et al*, Annals of Neurology 1990;**28**:393–5). Strange, I thought, I didn't know that convulsions with shigellosis were likely to recur. Well the point of the paper is to show that they aren't!

Fifty five children were followed up for between seven and 14 years. None had afebrile seizures and two had febrile convulsions in that time. Convulsions with shigella infection are different and do not carry the recurrence risk of febrile convulsions in general.

This paper opens up limitless possibilities for intriguing titles: 'Acrocephalopolysyndactyly in Prader-Willi syndrome'—it doesn't happen or 'Ochronosis following valproate therapy'—we've never seen it.

It could become a popular parlour game.

ARCHIVIST

Archives of Disease in Childhood 1991; **66:** 204–211

Outcome among surviving very low birthweight infants: a meta-analysis

Gabriel J Escobar, Benjamin Littenberg, Diana B Petitti

Abstract

Because published outcome studies are the only available source of data about the morbidity among surviving very low birthweight infants (VLBW, <1500 g) a search was carried out of 1136 references in the English language. A total of 111 outcome studies were found that reported morbidity data in cohorts of VLBW infants born since 1960. The methods used and results obtained in these studies were systematically assessed. No agreement exists about the definition of study populations, descriptive statistics, or measurement of outcome. Follow up ranged from six months to 14 years. In 85 cohorts the incidence of cerebral palsy was recorded, and in 106 that of disability. Studies that followed up infants for longer time periods reported higher incidences of disability. Studies from the United States reported higher incidences of disability than those from other countries. The median incidence of cerebral palsy among all the cohorts studied was 7·7%, and the median incidence of disability was 25·0%. Despite substantial improvements in the mortality of VLBW infants, poor outcomes among survivors are common.

During the past three decades, neonatal mortality among low birthweight (LBW, birth weight <2500 g) and very low birthweight (VLBW, birth weight <1500 g) infants has decreased dramatically.[1] This has resulted in ethical and economic problems, which are most acute with respect to the outcome of surviving VLBW infants.

Reductions in neonatal mortality associated with birth weight can be confirmed by analysis of data derived from large databases made up of birth and death certificates that are geographically based and centrally organised.[1–4] In contrast, no procedure for the follow up of surviving infants exists. Morbidity in VLBW survivors can only be inferred from published reports (outcome studies) from individual nurseries or multicentre perinatal studies, but these do not always set out explicitly to evaluate overall outcome. None the less, they are the only source of information on unselected cohorts of VLBW survivors and are widely cited in publications about health policy.[5–7]

It is critical to define rigorously the outcome of VLBW survivors. Parents deserve accurate prognostic information. Individual nurseries should evaluate their performance and the associations between changes in treatments and changes in morbidity. Regionally and nationally it is important to monitor the overall outcome of such infants so that plans for future services can be made; this is particularly important as care of VLBW infants is one of the most expensive items in paediatrics.[5 8 9]

When assessing outcome among VLBW infants, it is useful to pose questions that parents of such survivors might pose to a paediatrician: Will my child have cerebral palsy? Will my child be disabled? Will my child have learning difficulties or need special schooling? Answers to these questions are uncertain.

In the present study we asked the following questions:

- What are the characteristics of the methods used to evaluate the database from which inferences about outcome of VLBW infants were based?
- What inferences can be made about long term morbidity among these infants?

Methods

PUBLISHED REPORTS

We attempted to locate all the outcome studies written in English that reported cohorts of unselected VLBW infants born since 1960. Only data provided in the reports were considered; no attempt was made to contact the authors for missing data. We examined computer bibliographies, reference lists in textbooks and reviews, and consulted experts.

INCLUSION CRITERIA

To be included, a study had to have been published in English in a medical journal before 1 March 1988. Unpublished studies, abstracts, reports appearing only in government publications, summaries of presentations given at medical meetings, or brief transcripts of meetings, were excluded.

The study had to have presented primary data on the outcome of a cohort or cohorts of human infants weighing ≤1500 g at birth and born after 31 December 1959.

The study had not deliberately excluded infants in a non-random fashion, except those with lethal congenital anomalies, those small for gestational age, or those who were products of multiple births.

The study reported the number of babies eligible for evaluation (that is, the denominator).

It had to be possible to calculate the number of unevaluated babies (those lost to follow up) in the study.

The study had to have indicated at what age outcomes were assessed.

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All infants had to have been within the specified weight range at birth.

Randomised clinical trials meeting the above critieria were eligible for inclusion.

EXCLUSION CRITERIA

The following were excluded:

Studies that did not report new data, including review articles, letters, editorials, those limiting themselves to secondary data analysis, and those examining only mortality statistics.

Studies that were limited to analysis of technical, ethical, economic, or legal aspects of the management of newborns.

Studies in which data about VLBW infants was pooled with those about infants in higher weight ranges so that the outcome of those infants weighing ≤ 1500 g could not be abstracted independently.

Studies that excluded VLBW survivors without reporting the number of infants excluded so that it was not possible to calculate the denominator.

Studies in which the time period or location of the births that were reported could not be determined.

Studies in which data about infants born before 31 December 1959 were included in such a way that the outcome of infants born after that date could not be abstracted independently.

Studies that excluded infants in a non-random fashion such that the outcome of all VLBW infants at the study site could not be determined; this group included studies that followed only a selected group (for example, only mechanically ventilated infants or only those with cerebral palsy).

Anecdotal reports, or those reporting less than 10 births.

Studies limited to outcome during the time spent in hospital after the birth or limited to follow up by laboratory or radiological testing without giving clinical information about the affected infants' functions. For example, a study that simply listed the radiological presence of intraventricular haemorrhage was excluded, whereas a study that reported such infants' functional abilities was included. Similarly, studies that listed grades of retinopathy of prematurity but that did not actually mention whether children were blind were also excluded.

We retrieved and examined 1136 references. The 161 references that met the inclusion criteria were grouped into 111 studies or 'article clusters' as some studies comprised more than one article.

ABSTRACTION OF DATA

Data were abstracted in a computer compatible form; this was accurate enought for three people abstracting the same studies to agree on 95 to 100% of all items. All data were abstracted by a trained research assistant whose work was reviewed by one of us (GJE).

REVIEW OF METHODS USED

We defined 'reporting' as providing enough information for exact quantitation of a given description or outcome. If a study gave unquantifiable information (for example, 'many survivors . . .'), it was not considered as reporting a description or outcome. Various definitions of what constitutes cerebral palsy exist.[10] We recorded how many studies reported the presence of cerebral palsy, regardless of the definition given. We also recorded whether a 'global' (complete) assessment had been made. A study could report this in any one of three ways: firstly, specific terms were used that evaluated a survivor's performance in activities of daily living (for example, studies that reported numbers of 'severely handicapped' or 'completely normal' infants), whether or not these terms were defined. The second way to present enough information for the infants to be evaluated by at least two tests; for example, some studies provided information on the Bayley test and on the presence of cerebral palsy in varying degrees of severity so that one group of infants were defined as 'normal' and another as 'abnormal'. Thirdly, some studies simply referred to another scale of handicap or functional ability (for example, 'handicapped according to Saigal's criteria'), and these were considered to have carried out a complete assessment. If a study simply reported a result on one test (for example, 32% of infants failed to perform the Goodenough draw-a-person test), we did not consider this a complete assessment. This definition of complete assessment was imposed by the heterogeneity of the studies and is in itself a major problem in reports of outcome, which make no attempt to use standard definitions of impairments, disabilities, or handicaps.[11] For example, not all studies consider deafness, blindness, or cerebral palsy to be handicaps, and one study's criteria of 'minor' or 'moderate' might be considered to be 'severe' or 'extreme' by another.

Studies did not provide detailed information on how long they had followed up infants, making it impossible accurately to abstract well defined cohorts followed up for discrete periods of time. Consequently we could code only the stated, minimum, and maximum follow up periods. The stated follow up period was the time given in the title, abstract, or introduction. The minimum follow up was that of the infant(s) followed up for the shortest period, and the maximum was that of the infant(s) followed up for the longest period.

Data were compared by the χ^2 test with Yates's correction for continuity or Fisher's exact test, as appropriate. All p values are reported for two tailed comparisons.

CEREBRAL PALSY AND 'DISABILITY'

A cohort was defined as a group of VLBW survivors assembled at a specified time and place and followed up from birth to determine the morbidity. Generally, each eligible report studied one or more cohorts. To be eligible for this part of the analysis, a study had to have given data about infants in such a way that the outcomes of VLBW infants followed up for at least 12 months could be assessed independently of those followed up for less than 12 months. We abstracted data from all studies that reported incidences of cerebral palsy and from all studies that evaluated infants for the presence of a disability or handicap.

The following information was abstracted for each cohort: the weight range of the infants; whether the infants were excluded from receiving neonatal intensive care (however defined by the investigators); whether any attempt at impartial assessment took place; inclusion dates of the study; length of the minimum follow up period; definition of survivor; number of survivors; number of infants who died during the follow up period; number of infants listed as 'lost to follow up'; number of infants not evaluated; use of a geographically defined catchment area; and country of origin. In cases in which the report was ambiguous about the outcomes of some of the children studied or in which some infants were evaluated at less than 12 months of age, the infants were counted as 'not evaluated'.

In studies reporting the incidence of cerebral palsy, that for a given cohort was the number of infants with cerebral palsy divided by the total number of infants evaluated. In studies that reported complete assessments, we abstracted the number of infants that were considered 'normal', as well as how many had 'severe' or 'moderate' disabilities or handicaps, however defined. The incidence of 'disability' is thus defined as the number of infants with any disability or handicap divided by the total number of infants evaluated. We recognise that this use of the word 'disability' is not completely satisfactory.

For each subgroup of cohorts, the morbidity was determined by calculating the median and range of reported incidences, the mid-range of reported incidences (all reports between the 25th and 75th centiles that is, the middle two quartiles of the distribution of reported incidences), and the 95% confidence interval (CI) of the median.[12] The centiles and ranges show the distribution of reported results while the CI shows how close the median is to the mean. Because of a few reports of extremely high incidences, the median was usually less than the mean and therefore a more conservative estimate.

Differences between subgroups of cohorts were compared with the Mann-Whitney U test.[13] If more than two groups were compared, the median test was used.[14] The correlations between reported morbidity and continuous data (such as age at evaluation) were estimated by the Spearman rank correlation test.[13] We chose non-parametric tests because of the skewed distribution of many of the data.

Results

THE DATA

All the 111 studies that were included were from developed nations and reported 26 099 births world wide; 12 064 of these were from the United States. The studies fell into two broad categories: 98 (88%) were multiple outcome studies that purported to provide comprehensive information on VLBW survivors. Thirteen (12%) were limited outcome studies that explicitly set out to examine only one specific outcome—for example, the incidence of chronic lung disease among survivors. Ninety seven studies (87%) sampled infants at a single medical centre or perinatal clinic (single centre studies). In a small subset of these (n=4, 4% of the total) two such institutions had pooled their outcome results (cooperative studies). Fourteen (13%) defined a particular catchment area and attempted to locate all the infants in that area (geographic studies); seven of these reported all infants born in a defined area, and seven reported all infants born to mothers residing in a defined area. Although geographic studies made up only 13% of the total number of studies, they accounted for a quarter of the infants. Three of the 14 geographic studies were from the United States.

DEFINITIONS AND DESCRIPTIONS OF THE STUDY POPULATIONS

Nineteen different denominators were given, including live births, admissions within 24, 48, 72, or 96 hours of birth, survivors at 36 hours, and survivors at discharge. The following upper weight limits were given: 750, 800, 999, 1000, 1250, 1360, 1499, and 1500 g. Although not all studies reported the lower weight limit in their cohorts, we found no reference to a surviving infant weighing less than 500 g. Inclusion dates for infants varied considerably; some studies reported cohorts that had been gathered over periods longer than five years. Similarly, no agreement existed on how study populations should be described (table 1).

Only 10 studies (9%) provided sufficient information—number of live births, neonatal deaths, infant deaths, and post-infant deaths—that would permit comparison with databases of vital statistics. Only 53 (48%) of the studies provided any data on the infants' socioeconomic status. In 37 of these, enough data were given for us to work out whether the cohorts were composed predominantly of infants of low or high socioeconomic status. No study provided sufficient socioeconomic information to permit adequate comparison with another study.

INFANTS TRANSPORTED FROM OTHER HOSPITALS

Twenty seven of the studies (24%) reported only babies who were born at that centre and 43

Table 1 Description of study populations in 111 eligible studies

	No (%) of studies
No of studies reporting:	
Actual No of live births	26 (23)
No of deaths in delivery room	7 (6)
No of neonatal deaths	46 (41)
No of infant deaths	49 (44)
No of deaths in hospital	37 (33)
No of late deaths	50 (45)
No of small for gestational age infants	60 (54)
Breakdown of infants' gestational ages in increments of <4 weeks' duration	15 (14)
No of infants mechanically ventilated	56 (50)
Distribution by gender	57 (51)
Distribution by race	30 (27)
No of infants transported from other hospitals	70 (63)

(39%) reported on mixed groups, the percentage born in the centre ranging from 0 to 92%. Only one study permitted comparison of morbidity between those born at the referral centre and those born elsewhere. Forty one (37%) did not report how many infants had been transported.

TRACING INFANTS AND LENGTH OF FOLLOW UP

Only 15 of the studies (14%) used databases of vital statistics or home visits to track infants. The mean minimum follow up period was 24·8 months (range 1 to 168). The mean maximum follow up period was 51·7 months (range 4 to 224). Only 23 studies (21%) followed infants up for at least 36 months, and 19 (17%) included infants follow up for less than 12 months in their reported outcome rates.

Table 2 Characteristics of cohorts of VLBW survivors

	No of cohorts	*No of survivors*	*No of patients evaluated*
Studies evaluating infants for presence of cerebral palsy (n=85)			
Birth weight range (g)			
500 (±1) to 1500 (±1)	45	5024	4269
999 (±1) to 1500 (±1)	10	1044	901
500 (±1) to 1000 (±1)	15	782	665
500 (±1) to 1250 (±1)	8	501	406
500 (±1) to 750 (±50)	4	119	97
Miscellaneous	3	68	61
All VLBW infants	85	7538	6399
Definition of survivor			
Not specified	11	1009	787
Survived to discharge	32	2888	2495
Survived 7 days	2	17	17
Survived 28 days	31	2609	2158
Miscellaneous (range 70–1217 days)	9	1015	942
Studies performing a complete assessment of disability (n=106)			
Birth weight range (g)			
500 (±1) to 1500 (±1)	49	6014	4822
999 (±1) to 1500 (±1)	15	1436	1260
500 (±1) to 1000 (±1)	28	988	830
500 (±1) to 1250 (±1)	8	532	449
500 (±1) to 750 (±50)	4	95	78
Miscellaneous	2	37	35
All VLBW infants	106	9102	7474
Definition of survivor			
Not specified	21	1256	1001
Survived to discharge	41	3463	2949
Survived 7 days	2	31	31
Survived 28 days	32	2906	2385
Miscellaneous (range 70–1217 days)	10	1446	1108

DETERMINATION OF OUTCOME AND REPORTED OUTCOMES

Only one study compared a parent's assessment with that of a health professional. Forty one of the studies (37%) presented data obtained from comparison groups (for example, a matched group of infants born at term). Fifteen studies (14%) compared outcome in cohorts assembled in different time periods (historical controls). Thirty two of the 98 multiple outcome studies (33%) attempted to obtain impartial assessment (masking or blinding), and two of the 13 limited outcome studies (15%) did so. These figures may overestimate the use of masking, as any attempt at masking was coded as an impartial assessment. Studies varied widely in what they considered as 'masking': in some it was the data collector who was unaware of the group that the infant was in, but the person who actually assigned infants to outcome categories was aware of the infant's clinical course.

Many important outcomes were not reported. Among the 98 multiple outcome studies, incidences of cerebral palsy were reported by 74 (76%), blindness by 70 (71%), deafness by 61 (62%), and sudden infant death syndrome by 47 (48%). Studies from the United States were less likely to report these outcomes than those from other countries (p values ranged from 0·0005 to 0·068).

We compared the 53 studies published before 1983 with the 58 published in 1983 and since. There were no significant differences between the two periods in methods of sampling or ascertainment, reporting of descriptions or outcomes, or length of follow up.

Of the 111 studies in the data set, 82 (74%) carried out complete assessments, 75 (68%) reported the incidence of cerebral palsy, and 67 (60%) did both. The 85 cohorts that reported on cerebral palsy included 7538 surviving infants of whom 6399 were actually evaluated at the age of 12 months or more; the percentages lost to follow up ranged from 0 to 53% (median 10·9%). The 106 cohorts that reported the incidence of disabilities included 9102 surviving infants of whom 7474 were actually evaluated at

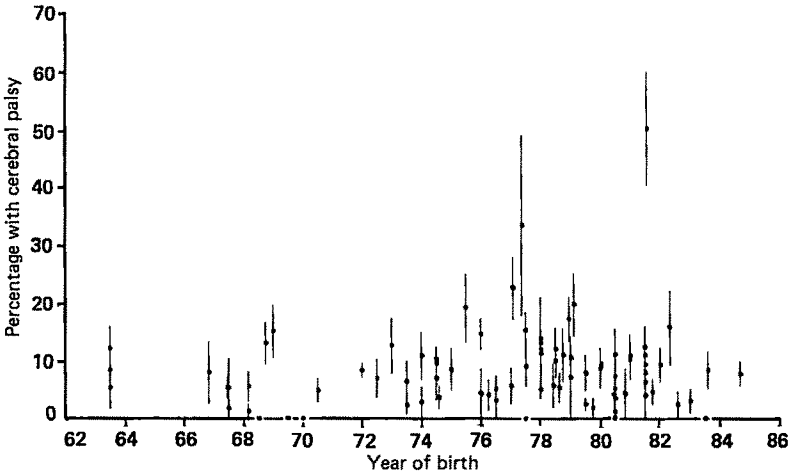

Figure 1 Incidence of cerebral palsy among VLBW survivors. The vertical axis represents the reported incidence for each of 85 eligible cohorts. The horizontal axis indicates the midpoint of the period of enrollment. Each bar represents the mean (SD) rate of a single cohort of subjects.

Table 3 Reported incidences of cerebral palsy

Subgroup	*No of cohorts*	*Median (%)*	*95% CI*	*Range*	*p Value*
All cohorts	85	7·7	5·3 to 9·0	0–50·0	
*No of survivors evaluated:					
<67	44	6·6	4·4 to 10·6	0–50·0	0·48
≥67	41	8·3	5·3 to 9·4	1·1–17·1	
*No of survivors/year:					
<25	41	5·3	3·0 to 8·0	0–33·3	0·002
≥25	44	9·1	7·3 to 10·6	2·4–50·0	
Midpoint of enrollment:					
1960–1977	40	6·0	4·9 to 8·5	0–33·3	0·30
1978–1986	45	8·0	5·7 to 10·1	0–50·0	
Country of birth:					
United States	29	5·7	4·6 to 11·1	0–50·0	0·72
Other	56	7·9	5·7 to 9·0	0–33·3	
Length of follow up (months):					
<24	43	6·4	4·4 to 8·3	0–22·4	0·13
≥24	42	8·4	5·6 to 10·4	0–50·0	

*The median cohort size was 67. The median number of VLBW survivors/year was 25. Results of additional subgroup analyses available from the authors.

the age of 12 months or more; the percentages lost to follow up ranged from 0 to 55% (median 11·3%) (table 2).

CEREBRAL PALSY AND DISABILITY AMONG VLBW SURVIVORS

The reported incidences of cerebral palsy and some subgroup analyses are shown in fig 1 and table 3. The median among all the cohorts studied was 7·7% (CI 5·3 to 9·0). There was no improvment in incidence with time (fig 1). The incidence of cerebral palsy did not differ between small and large cohorts. There were, however, significant increases in reported incidence of cerebral palsy as the number of infants who were enrolled increased (Spearman rank correlation test, $p=0{\cdot}002$). Likewise, the numbers of survivors evaluated and of VLBW survivors/year (a possible marker for experience or volume of care) correlated positively with the incidence of cerebral palsy. No other differences were significant.

Table 4 Reported incidences of disability

Subgroup	*No of cohorts*	*Median (%)*	*95% CI*	*Range*	*p Value*
All cohorts	106	25·0	20·9 to 30·0	0·0–80·0	
*No of survivors evaluated:					
<50	53	29·8	21·4 to 34·8	0·0–80·0	0·02
≥50	53	21·2	15·9 to 28·3	6·0–60·8	
*No of survivors/year:					
<23	52	30·0	21·4 to 37·4	5·9–80·0	0·02
≥23	54	21·2	17·9 to 27·3	0·0–56·8	
Midpoint of enrollment:					
1960–77	55	29·8	21·2 to 37·3	0·0–80·0	0·04
1978–86	51	21·4	18·8 to 29·3	6·0–57·7	
Country of birth:					
United States	44	30·0	25·0 to 37·9	7·1–80·0	0·002
Other	62	20·5	15·8 to 28·1	0·0–73·7	
Length of follow up (months):					
<24	57	21·5	19·6 to 27·3	0·0–57·1	0·06
≥24	49	33·6	18·8 to 39·4	5·9–80·0	

*The median cohort size was 50. The median number of VLBW survivors/year was 23. Results of additional subgroup analyses available from the authors.

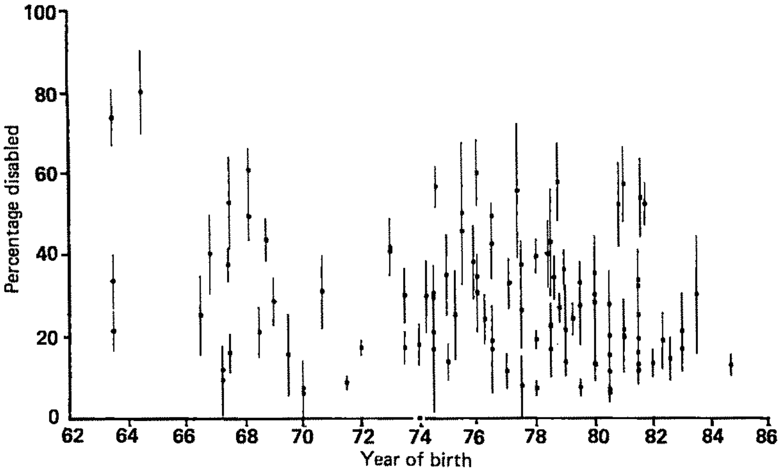

Figure 2 Incidence of disability among VLBW survivors. The vertical axis represents the reported incidence for each of 106 eligible cohorts. The horizontal axis indicates the midpoint of the period of enrollment. Each bar represents the mean (SD) rate of a single cohort of subjects.

The median incidence of disabilities (table 4 and fig 2) among all eligible cohorts was 25·0% (CI 20·9 to 30·0). The incidences were significantly higher among the studies from the United States than those from other countries. In contrast to the results concerning cerebral palsy, incidences were lower in larger and more recent cohorts and in centres that enrolled more survivors/year. Studies that followed children up for longer periods tended to report higher disability rates. Cohorts of high socioeconomic status had lower rates of disability than those of low status but this was not significant. Cohorts for which socioeconomic data could not be extracted ($n=64$), however, had significantly lower incidences of disability than those with either high ($n=18$) or low ($n=24$) status ($p=0{\cdot}011$).

Notably there was no difference between reported incidences of cerebral palsy or disabilities in cohorts of infants weighing less than 1000 g at birth and those between 1000 and 1500 g (table 5).

Tests of correlation confirmed the trends noted in the subgroup analyses of incidences of disabilities. There were significant negative correlations between the incidence of disabilities with mid-year of enrollment period, number of survivors enrolled, number of survivors evaluated, and number of survivors enrolled each year. There was a highly significant positive correlation between incidence of disability and length of follow up. Studies with the highest incidences of disability did not differ significantly in methods of reporting when compared with studies with the lowest incidences.

Discussion

In considering the reported fate of surviving VLBW infants, one must first consider how the population was defined: what was the denomi-

Table 5 Influence of birth weight on rates of cerebral palsy and disability

	Birth weight (g)			
	0–1500	*1000–1500*	*0–1000*	*Other ranges*
Incidence of cerebral palsy*				
No of cohorts	45	10	15	15
Median (%)	8·3	6·4	7·0	4·4
95% CI	5·7 to 10·1	1·1 to 12·9	4·4 to 10·9	2·4–9·8
Range	0–22·4	0–33·3	0–15·1	0–50·0
Incidence of disability**				
No of cohorts	49	15	28	14
Median (%)	20·9	22·6	27·4	30·0
95% CI	17·1 to 32·9	11·7 to 39·4	20·0 to 30·8	21·4–57·1
Range	0–80	6·8–60·8	9·1–60·0	14·3–73·7

Four way comparison: *p=0·36; **p=0·59.

Table 6 Estimates of incidence of cerebral palsy in VLBW infants

Study	*Birth years*	*Denominator*	*Age at follow up (years)*	*Percentage incidence of cerebral palsy*
Stanley and Watson[26]	1968–81	Live births	5	1·4–2·7
Stanley and Watson[26]	1968–71	Survivors at 28 days	5	4·4
Stanley and Watson[26]	1972–74	Survivors at 28 days	5	4·6
Stanley and Watson[26]	1975–78	Survivors at 28 days	5	2·8
Stanley and Watson[26]	1979–81	Survivors at 28 days	5	3·8
Hagberg *et al*[28 29]	1963–66	Survivors at 7 days	4	6·9
Hagberg *et al*[28 29]	1967–70	Survivors at 7 days	4	4·5
Hagberg *et al*[28 29]	1971–74	Survivors at 7 days	4	6·0
Hagberg *et al*[28 29]	1975–78	Survivors at 7 days	4	5·4
Hagberg *et al*[28 29]	1979–82	Survivors at 7 days	4	8·0
NCPP[27]	1959–66	Survivors at 1 year	7	9·0
Present study	1960–85	See text	≥1	7·7

Stanley and Watson reported a prevalence survey from Western Australia.[26] Hagberg *et al* reported case control studies from Sweden.[27 28] The National Collaborative Perinatal Project (NCPP)[27] was a cohort study that orginally included 304 VLBW infants; results shown here are based on 188 survivors at 1 year.

nator? The incidence of any outcome is strongly dependent on the denominator used.[10 15] The characteristics of the population are also important, particularly with respect to the numbers of infants transferred from other hospitals[16 17] and the distribution of gestational ages.[5 18]

Once a population is defined, it is necessary to decide what outcomes are to be measured. Because the list of possible outcomes to measure is infinite, it is important to consider those conditions that will be relevant to survivors, their parents, health care providers, and planners. Though this point seems obvious, it has not always been considered in reports of outcome. At the least, one wants to know how many VLBW survivors have cerebral palsy, are blind, deaf, or will need special schooling.

The length of the follow up period is critical because some conditions present late. For example, the Western Australia cerebral palsy register has reported that 30% of cases of cerebral palsy are diagnosed after the age of 2 years.[19] In the United States, Palfrey *et al* found that only 28·7% of children with special needs were identified before the age of 5 years.[20] These results are supported by our findings. As infants get older, the role of their socioeconomic status in determining their outcome might increase; Palfrey *et al* found that maternal education was a significant predictor of age at identification.[20]

In addition, tracing of infants becomes more difficult over time. It is not clear what sort of infants are most likely to be lost to follow up. Tyson *et al* suggested that, at least with respect to infants in lower socioeconomic groups, untraced survivors may be equally as likely to be handicapped as those who are evaluated.[21] Wariyar and Richmond, in a study that achieved 100% follow up, reported significantly higher disability rates among those infants who were more difficult to trace.[22] Time is also important when comparing studies, because standards of care change.

Who evaluates infants is also important. Observers may be biased when evaluating infants whose medical history is known, or who they have cared for personally. Similarly, parents actually caring for handicapped infants may have different perceptions of the severity of a particular child's handicap than a neonatologist. It is to avoid such biases that most investigators consider it important to ensure impartial observers.[10 23 24]

Finally, once the incidence of a given outcome is determined, it is important to ask what this means and how it relates to the general population. It is important to compare outcomes with those of term infants,[23] as there are published data on the prevalence of such outcomes in the general population.[10 19 25–31]

The following conclusions can be made about published reports about the outcome for VLBW infants:

(i) The database is small. We could only locate reports on 26 000 babies in almost 30 years—but each year almost 40 000 are born in the United States alone. The number of infants actually evaluated for outcomes such as cerebral palsy was even smaller, roughly 7000 infants. Even fewer infants were followed up until school age, and the number of infants born weighing less than 1000 g who were evaluated was less than 1000.

(ii) There was no agreement on what should be the appropriate denominator. This not only limited the value of comparisons between studies, but also precluded comparison with databases of vital statistics, which are based on numbers of live births.

(iii) Although morbidity among surivors is often at the centre of ethical debates, it is striking that there is no agreement as to what constitutes an adverse outcome. Conditions such as blindness, deafness, and cerebral palsy were not always reported or were considered to be of minor importance.

(iv) Most of the published reports consist of data on infants followed up for less than three years. Furthermore, because of inconsistent reporting, little attention paid to preventing selection or ascertainment biases, and little use of impartial observers, it seems likely that the reports underestimate the morbidity among these infants.

(v) Little improvement in the methods of carrying out these studies has taken place over time.

With respect to the actual outcome of VLBW survivors, the following inferences can be made:

(i) The most striking aspect of the papers that we reviewed was the tremendous variation among the outcomes reported, with studies in the same time period reporting widely divergent results. This heterogeneity was similar to that noted among internursery comparisons of mortality and incidences of chronic lung disease.[32–34]

(ii) The median incidence of cerebral palsy reported among all the cohorts studied was 7·7% and showed little variation over time; this figure is similar to those given in other studies (table 6). If one assumes the incidence of cerebral palsy in the general population to be 2/1000 live births or neonatal survivors (a generally accepted estimate[25]) then the relative risk for cerebral palsy among surviving VLBW infants would be 38 times that in the general population.

(iii) Our best estimate for the incidence of disability in VLBW survivors in these reports is about 25%. Because studies did not uniformly report adverse outcomes, particularly lung disease, this figure may be an underestimate. Furthermore, we think that evaluation at too young an age may be resulting in an incorrectly low incidence being reported. As other birthweight specific databases do not exist, external confirmation or refutation of this estimate is currently impossible. The reported incidence of disability varies from centre to centre, and is related to the size of the study, the age at which the children are evaluated, and the date of the midpoint of a study's enrollment period.

(iv) Also striking is the increased incidence of disability reported in studies that followed up infants for longer periods of time, an issue raised by other investigators.[35] This finding is all the more remarkable when one considers the crudity of our measure for length of follow up: for this analysis, we could code only the minimum follow up period for each cohort.

(v) The surprising finding that studies from the United States report higher incidences of disabilities, though statistically robust, awaits independent validation in studies using uniform criteria for the denominators and outcome measures.

THE LIMITATIONS OF THIS ANALYSIS

Many of the subgroup analyses were designed to assess impact of study design on reported outcome. It is surprising to us that morbidity did not differ with the use of geographic inclusion criteria or of impartial evaluators, or that it did not differ among cohorts of different birth weights. Many of our subgroup analyses had only borderline significance. Furthermore, the fact that we tested multiple comparisons means that the calculated p values may be misleading. As we performed 16 tests of significance on each outcome, a conservative analysis would set the threshold for significance at $0{\cdot}05/16=0{\cdot}003$. In this case, only our strongest findings among subgroups (that studies from the United States reported higher incidences of disability than those from other countries and that centres with larger numbers of VLBW infants report higher incidences of cerebral palsy) would be called 'statistically significant'.

The most important limitation, however, is in the data themselves: the figures that we have derived can only be considered crude estimates because of the limitations inherent in the studies themselves. It is important to remember that, even to make these crude estimates, it was necessary to make a number of simplifications—such as assuming that one can pool results based on 28 day survivors with those using survivors of unspecified duration. Furthermore, the imprecision of the methods used in the studies undoubtedly affected our results. For example, when considering variations in reported incidences of disability over time one must keep in mind that the studies reported enrollment periods ranging from 8 months to 16 years.

The striking finding of a 50% greater rate of disability among babies studied in the United States compared with those born in other countries does not seem to be the result of differences in the definitions of disability. We cannot discern from our data if this association is the result of differences in health care technology or delivery around the world, differences in the definition of disability across countries, or differences in the biology or mortality of VLBW in the different centres. Nurseries in the United States may be more aggressive than those in other countries in treating the highest risk infants, and thus be prone to greater morbidity.[36]

Before ascribing too much meaning to this finding, however, one must consider some limitations in our analysis. Firstly, we excluded studies not published in English. Secondly, our estimates were based on a small number of infants and spanned several decades. Further refinement of our estimates using available data would be difficult. For example, one might wish to include only studies that included babies born after 1980—a reasonable approach in the light of recent changes in the care of these infants. Only 21 cohorts would be available, with a total of 1408 babies evaluated. Should one generalise to the population of VLBW infants at large after studying only 1408 infants?

Moreover, whereas some comparison is possible with other studies of the incidence of cerebral palsy, no such comparison is possible of handicap, as other birthweight specific databases do not exist. For example, a frequently cited source on morbidity among all children in the United States (the Child Health Supplement of the National Health Interview Survey) includes only 90 VLBW infants, all of whose weights were determined by maternal recall.[37] A recent meta-analysis of LBW outcome studies focused on intelligence and developmental quotients, and did not mention the question of what the incidence of cerebral palsy or disability was among these infants.[38]

Recommendations

(1) Evaluation of the outcome of VLBW survivors should be given priority in paediatric research.

(2) National paediatric and medical associations, as well as the editorial boards of important medical journals, should establish minimum standards for the design, conduct, and reporting of outcome of VLBW survivors. Standards should be set that deal with the

concerns about different methods that have been raised in this analysis and by other investigators.[6 17 21 38 39]

(3) National paediatric and medical associations should encourage the development of geographically based birth weight specific morbidity databases so monitoring of the overall outcome of VLBW infants is possible.

(4) Outcome studies should be prospective, use impartial observers, include full term infants as controls, and include assessments of the parents of VLBW survivors.

(5) Agreement on defining outcome measures, even crude ones, must be reached so that studies can be compared. The experience of population based cerebral palsy registries should be used as models.

(6) Institutional incentives and funding must be offered so that follow up of VLBW survivors, particularly multicentre and geographical studies, is financially and professionally feasible. Both the confidentiality of patients and the protection of physicians from allegations of malpractice must be assured by each institution.

Despite the increased survival of VLBW infants, it is extremely difficult to know how the survivors are faring. This problem has been ignored in discussions about whether individual infants should receive 'heroic' care or whether the '800 gram barrier' can be broken.[5] Our ability to assess and report the outcome of surviving VLBW infants has lagged behind our willingness to resuscitate them.

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Holidays and atopic eczema

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Abstract

Information was collected by telephone about 300 holidays taken over a three year period by 126 children with severe atopic eczema. During the holidays, improvement in eczema occurred more frequently (112/300, 37%) than deterioration (63/300, 21%). There was a significant correlation between improvement and a more southerly holiday location: improvement was common in holidays taken in the Mediterranean or further south (63/92, 69%), but holidays in northern Britain were more likely to be associated with deterioration (27/100, 27%) than improvement (13/100, 13%). Changes in eczema were correlated with changes in asthma in 231 holidays taken by children with both conditions, but improvement was not significantly associated with pet ownership. All patients returned to their preholiday state, usually within two weeks of return home. The causes of changes in eczema while on holiday have not been identified.

Triggers that worsen atopic eczema tend to be uppermost in the minds of parents and doctors. Things which are associated with improvement are often overlooked. This may explain the fact that although the most severe skin lesions may dramatically improve when the patient goes on holiday, changes in eczema associated with holidays do not appear to have been studied before. We conducted a telephone survey to investigate the effect of holidays on atopic eczema.

Patients and methods

The survey was conducted by MAT in November 1989. At that time, 188 children with atopic eczema were frequently (at least every three months) attending the University Department of Child Health. Eight, who no longer had eczema and who were still attending because of asthma, were excluded. For 154 children a telephone number was known, and by making up to two calls to each number the parents of 136 children were contacted. Ten children had taken no holidays in the period of the survey. All parents contacted agreed to participate, and were asked a standard set of questions about all holidays taken by the patient during 1987, 1988, and 1989.

Results

Data on 300 holidays taken by the 126 patients were collected. This included three affected younger siblings of index cases who between them had five holidays. The median number of holidays per patient was 2 (range 1–6). The median age at the time of the holiday was 6·7 years (range 0·4–18·5). Holiday locations were classified by latitude (table 1). All holidays were taken in the summer—it so happened that there were no winter or skiing holidays. Change in eczema severity was reported as much better on 67 (22%) holidays, slightly better on 45 (15%), no change on 125 (42%), slightly worse on 39% (13%), and much worse on 24 (8%). Improvement was significantly more common than deterioration (sign test $p<0·01$).

Table 1 Holiday location

Zone	*Latitude (degrees north)**	*Locations*	*No of holidays*
A	>52	Scotland, northern England, north Wales	100
B	50–52	Southern England, south Wales	92
C	48–50	Northern France	14
D	45–48	Switzerland	2
E	40–45	Southern France, Yugoslavia	16
F	35–40	Spain, Portugal, Balearics, Greece	63
G	25–30	Florida, Canaries, Pakistan, Bangladesh	12
H	<25	Malaysia	1

*Manchester is 53·5° north.

TIMING OF CHANGES

In the 112 holidays where the eczema improved, this improvement occurred within two days of the start of the holiday in 10 (9%), between the second and fourth day in 53 (47%), between the fifth and seventh day in 32 (29%), and after the seventh day in six (5%). In the 63 holidays with deterioration in the skin, this occurred within two days in 20 (32%), between the second and fourth day in 23 (37%), between the fifth and seventh day in five (8%), and after the seventh day in two (3%). (The timing could not be recalled in 11 holidays with improvement and 13 with deterioration.) Deterioration therefore occurred more rapidly than did improvement ($p<0·001$, Mann-Whitney U test).

HOLIDAY LOCATION

Table 2 shows change in eczema for each zone of latitude. Only in zone A (northern Britain) was deterioration more common than improvement ($p=0·05$, sign test). Improvement correlated with more southerly holiday destination (Spearman rank correlation coefficient $r_s=0·42$, $p<0·001$). The data include more than one holiday for many of the individuals and so are not truly independent. To investigate this, patients

Table 2 Change in eczema by zone. Results are number (%) of holidays

Zone	*Much better*	*Slightly better*	*No change*	*Slightly worse*	*Much worse*	*Total*
A	5 (5)	8 (8)	60 (60)	17 (17)	10 (10)	100
B	14 (15)	17 (18)	38 (41)	14 (15)	9 (10)	92
C	2 (14)	3 (21)	6 (43)	2 (14)	1 (7)	14
D	0	0	0	1	1	2
E	2 (12)	7 (44)	5 (31)	2 (12)	0	16
F	37 (59)	9 (14)	13 (21)	2 (3)	2 (3)	63
G	7 (58)	1 (8)	2 (17)	1 (8)	1 (8)	12
H	0	0	1	0	0	1
Total	67 (22)	45 (15)	125 (42)	39 (13)	24 (8)	300

who took two or more holidays were examined. There were 91 who took two or more holidays, and in these the two most recent holidays were in the same zone in 44 (48%) ($r_s=0{\cdot}43$, $p<0{\cdot}001$). However, taking the most recent holiday for each patient, there was still a significant correlation between latitude and improvement ($r_s=0{\cdot}50$, $p<0{\cdot}001$). Patients appeared to react consistently to successive holidays in the same zone. Forty four patients took their two most recent holidays in the same zone. Of the 14 who improved on the penultimate holiday, 11 (79%) also improved on the latest holiday. The outcomes of the two most recent holidays in this group of 44 patients were significantly correlated ($r_s=0{\cdot}46$, $p<0{\cdot}01$).

It might be suggested that changes in eczema severity on one holiday would influence the subsequent choice of holiday destination, and that those who improved in a particular zone would be more likely to return to that zone than those who deteriorated. This did not appear to be the case. Of the 90 patients who took two or more holidays, 32 improved on their penultimate holiday. Only 14 of these (44%) returned to the same zone, while 30 of the 59 (51%) who did not improve returned to the same zone for their latest holiday. This difference was not significant ($p>0{\cdot}1$, Mann-Whitney U test).

DURATION OF HOLIDAY

Altogether 144 (48%) of the holidays were of 10 days or greater duration. Improvement was more likely in these holidays than in the 156 of less than 10 days ($p<0{\cdot}001$, Mann-Whitney U test). However, duration also correlated with more southerly destination ($p<0{\cdot}001$, Mann-Whitney U test), and when the association between outcome and duration of holiday was examined for each zone of latitude separately, correlation was found only within zone B (southern Britain), where improvement was more likely on longer holidays ($p<0{\cdot}01$, Mann-Whitney U test).

OTHER ATOPIC DISEASE

In the 231 holidays taken by patients who also had asthma, improvement in asthma correlated with improvement in eczema as shown in table 3 ($r_s=0{\cdot}44$, $p<0{\cdot}001$) and with more southerly destination as shown in table 4 ($r_s=0{\cdot}27$, $p<0{\cdot}001$). In 22 holidays taken by patients with rhinitis, improvement was noted in 13 and worsening in nine. Improvement in eczema was more likely in the 13 patients whose rhinitis improved than in the nine whose rhinitis deteriorated ($p<0{\cdot}01$, Mann-Whitney U test). On 84 holidays the patient was accompanied by a parent with atopic disease (eczema, asthma, or rhinitis). Change in the parents' symptoms correlated with change in the child's eczema ($r_s=0{\cdot}25$, $p=0{\cdot}02$).

Table 3 Change in eczema in relation to change in asthma. Results are number of holidays

	Asthma					
	Much better	*Slightly better*	*No change*	*Slightly worse*	*Much worse*	*Total*
Eczema:						
Much better	10	8	32	3	0	53
Slightly better	1	2	31	2	0	36
No change	0	1	87	4	1	93
Slighty worse	0	0	19	6	4	29
Much worse	0	0	14	4	2	20
Total	11	11	183	19	7	231

Table 4 Change in asthma by zone. Results are number (%) of holidays

Zone	*Much better*	*Slightly better*	*No change*	*Slightly worse*	*Much worse*	*Total*
A	0	1 (1)	65 (84)	7 (9)	4 (5)	77
B	1 (1)	2 (3)	63 (85)	7 (9)	1 (1)	74
C	2 (18)	0	8 (73)	0	1 (9)	11
D	0	0	2	0	0	2
E	0	1 (10)	8 (80)	0	1 (10)	10
F	6 (13)	4 (9)	31 (67)	5 (11)	0	46
G	2 (20)	3 (30)	5 (50)	0	0	10
H	0	0	1	0	0	1
Total	11 (5)	11 (5)	183 (79)	19 (8)	7 (3)	231

PETS

In 85 holidays the patient left a home containing a mammalian or avian pet for holiday accommodation that was free of animals. Improvement was more likely (49%) in this group than in the remaining 215 (33%), $p<0{\cdot}01$, Mann-Whitney U test. However, pet owners were more likely to travel further south for holidays ($p<0{\cdot}05$, Mann-Whitney U test) and when pet withdrawal was examined for each zone separately, there was no significant difference in outcome ($p<0{\cdot}1$, Mann-Whitney U test). In 55 holidays the pet left at home was a cat or a dog. Improvement occurred in 44% of this group compared with 36% of the other 245. This difference was not significant ($p>0{\cdot}1$, Mann-Whitney U test).

AGE OF PATIENT

Improvement in eczema was more likely with increasing age ($r_s=0{\cdot}16$, $p=0{\cdot}007$), but older children were more likely to holiday further south ($r_s=0{\cdot}11$, $p=0{\cdot}05$) and when examined by latitude zone there was no correlation between age and outcome.

TREATMENT

Topical treatment was increased on 16 holidays and decreased on 10. Increasing treatment correlated with deterioration while on holiday ($r_s=0{\cdot}30$, $p<0{\cdot}001$). Patients were on a restricted diet for 221 (74%) of the 300 holidays. Parents admitted that foods normally disallowed were consumed during 24 of these holidays, but there was no significant difference in outcome ($p>0\cdot1$, Mann-Whitney U test).

SEA AND POOL BATHING

Patients sea bathed on most days in 51 (17%) and on some days in 41 (14%) of the holidays. The frequency of sea bathing correlated with improvement ($r_s=0\cdot30$, $p<0\cdot001$) but also with more southerly holidays ($r_s=0\cdot22$, $p<0\cdot001$). When the association between sea bathing and change in eczema was examined for each zone separately, no correlation was found except in zone B (southern Britain), where improvement correlated with sea bathing ($r_s=0\cdot30$, $p<0\cdot01$). Swimming pools were used on most days in 79 (26%) and on some days in 47 (16%) of holidays. Swimming pool use was correlated with improvement ($r_s=0\cdot27$, $p<0\cdot001$), but also with more southerly destinations ($r_s=0\cdot40$, $p<0\cdot001$). When the association between swimming pool use and change in eczema was examined for each zone separately, no correlation was found except in zone F (Iberia and Greece), where improvement correlated with swimming pool use ($r_s=0\cdot30$, $p<0\cdot02$).

SUNSCREEN

A sunblocking oil or cream was used on 109 (36%) of holidays. Improvement was more likely when sunscreen was used ($p<0\cdot01$, Mann-Whitney U test), but sunscreen use was more common in more southerly locations ($p<0\cdot001$, Mann-Whitney U test), and when the zones were examined separately, the correlation between sunscreen use and improvement was found only in zone B ($p<0\cdot05$, Mann-Whitney U test).

PARENTS' OBSERVATIONS

The parents were asked which factors they felt were the most important causes of change in their child's eczema while on holiday (more than one reason could be given). In the 112 holidays where an improvement was noted, sunshine was thought to be important in 53 (47%), 'change of air' in 33 (29%), sea bathing in 32 (29%), psychological factors in 15 (13%), and change of diet in two (2%). Parents could think of no reason for change in 26 (23%).

In the 63 holidays where the child's eczema deteriorated, change of air was thought to be important in 19 (30%), contact with sand in 14 (22%), sea bathing in 13 (21%), sunshine in 10 (16%), psychological factors in eight (13%), and change of diet in four (6%). In 10 (16%) no reason could be given for deterioration.

SAND

The patients had contact with sand in 172 holidays. The parents noted that contact with both wet and dry sand caused an increase in symptoms of eczema in 74 holidays (43%) and wet sand only in 26 holidays (15%). No effect was seen in 65 (38%), and in seven holidays (4%) exposure to sand was thought to reduce symptoms.

USUAL RESPONSE TO WEATHER

The parents were asked about the child's usual response to changes in weather while at home. Altogether 62 holidays (21%) were taken by children who were reported not to react to changes in weather, 52 (17%) who reacted adversely to cold weather only, 96 (32%) to hot weather only, 33 (11%) to both hot and cold weather, and 56 (19%) to any change in weather. To investigate whether changes in eczema while on holiday were related to previously noted reactions to hot weather, the 114 holidays taken by patients who did not react, or reacted to cold weather only, were compared with the other 185. No significant difference in outcome was found ($p>0\cdot01$, Mann-Whitney U test).

RETURN HOME

After all 175 holidays in which the eczema had changed the patients' eczema returned eventually to its preholiday state. This occurred within two days of return from five holidays (3%), between two and four days in 23 (13%), between five and seven days in 33 (19%), between eight and 14 days in 29 (17%), and after 14 days in 55 (31%). The timing of return to normal could not be recalled in 30 holidays. No patient had a permanent improvement, and no patient who had improved on holiday became worse than usual after return.

Discussion

Although textbooks report that up to 10% of patients with atopic eczema deteriorate during the summer due to exposure to sunlight,[1] in this study children with eczema were more likely to improve than to deteriorate while on holiday, and the tendency to improve was more noticeable in holiday destinations at southern latitudes. For example, considerable improvement was seen during 75% of holidays taken in the Balearics, 54% in mainland Spain, and 47% in Greece. By contrast, only 4% of holidays in north Wales and 7% in northern England resulted in appreciable improvement. Deterioration was seen in 26% of holidays in Britain and in only 9% of Mediterranean holidays.

A possible explanation of improvement while on holiday is the beneficial effect of ultraviolet light on atopic eczema.[2-5] However, latitude is only a crude measure of exposure to ultraviolet light. The amount of light in a particular location is also influenced by the time of year and the number of hours of cloud free sunshine, and an individual's exposure is further modified by duration of outdoor activity and shielding by clothes and topical sunscreens. In favour of the beneficial effect of sunshine was the observation that improvement correlated with sea bathing and sunscreen use within zone B (southern Britain). This area has a much more variable summer weather pattern than, for example, the Mediterranean area, and these two activities may be markers of holidays with more sunshine exposure. Sunshine was the factor most likely to be mentioned by parents as a cause of improvement. However it is less easy to see how sunshine could explain improvement in asthma.

Another possible explanation for improvement with increasing distance from home is a change in amount or type of environmental allergens, such as house dust mite or pet epithelium. There is a lack of data about geographical variation in house dust mite numbers, and an individual's exposure to this or other mites is influenced by factors such as amount of time spent indoors, type of bedding and floor covering, as well as the frequency and method of cleaning. We could therefore draw no conclusions about the effect of house dust mites from our data, but the importance of environmental allergens is possibly supported by the findings of a correlation between improvement in eczema and change in asthma and rhinitis. Removal of the patient from a home containing pets did not appear to have a significant effect on outcome.

It is impossible, in a study of this nature, to quantify psychological variables such as degree of distraction or reduction in stress. Such factors were thought to be important by parents in only 13% of holidays where improvement was seen, and in a similar proportion of holidays with deterioration. Psychological factors would not easily explain the appreciable association between improvement and latitude. Lapses in treatment (topical or dietary) are likely to have been under-reported, but there was no effect of reported dietary indiscretions. The correlation of increased topical treatment with deterioration suggests that changes in treatment are the result of, rather than the cause of, changes in eczema severity.

A drawback to this study is the non-independence of the 300 holidays taken by the 126 children. Although the findings were similar when the patients' most recent holidays were analysed separately, the choice of location is likely to have been influenced by previous holiday experience, and there was no way that this source of bias could be excluded. The choice of resorts (for example, lack of winter holidays) probably reflects the holiday preferences of the local population. A further drawback is the retrospective nature of the study. It is possible that some parents expect the eczema to improve on holidays, in which case they may tend to remember improvement rather than deterioration. This does not fully explain the effect of latitude, however, and it is not consistent with the numerous preholiday inquiries we receive about sunscreens and possible exacerbation of eczema due to sunlight.

In conclusion, holidays taken in the Mediterranean or further south were often (69%) associated with improvement in atopic eczema. Holidays taken in southern Britain were sometimes (34%) associated with improvement, particularly if taken for 10 days or more, and if the weather permitted sea bathing and sunscreen use. Holidays in northern Britain were more likely to be associated with deterioration (27%) than improvement (13%). The effect of holidays was usually short lived, the skin condition reverting to the preholiday state within two weeks of return. The causes of the changes associated with holidays have not been identified.

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Hydration in severe acute asthma

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Abstract

Twenty children were studied during severe attacks of acute asthma to find out how dehydrated they were on admission to hospital. Mean body weight on admission was 97·8% of their reference stable weight seven to 10 days after the attack and in only three children was it less than 95% of the stable weight. Bedside assessment of dehydration was unreliable. The mean packed cell volume was significantly higher on admission than 7–10 days later (0·44 compared with 0·42, difference 0·02 SE 0·01). Serum sodium and potassium concentrations and osmolality on admission were within normal ranges. The degree of dehydration correlated best with a fall in blood pH. There was no association between the degree of dehydration and the recovery of the peak expiratory flow rate during the first 24 hours or thereafter. We conclude that mild dehydration is common in severe acute childhood asthma. Fluid given at a rate of 50 ml/kg/24 hours was safe and appropriate for these children.

Treatment with intravenous fluid replacement is considered to be an important part of the management of severe acute asthma,[1] but there is no consensus about the volume that should be given during the acute phase. There are two contrasting approaches; the first, based on the results of adult studies, is that patients with severe asthma become appreciably dehydrated and that the degree of dehydration is directly related to the severity and duration of the attack.[2–4] Liberal correction of fluid deficits is thought to mobilise mucus plugs and to decrease narrowing of airways.[5 6] The second approach, assumes that appreciable dehydration is not a feature of asthma and that indiscriminate correction of fluid deficits in patients having severe attacks may be harmful. This approach is largely based on the finding of raised concentrations of antidiuretic hormone in patients with acute asthma.[7 8] Giving unnecessary additional fluids to such a patient could lead to fluid retention, pulmonary oedema, and deterioration in the patient's condition. This is particularly so if the increase in antidiuretic hormone represents an appropriate response to mild dehydration. The value of the measurement of acute weight changes as an index of dehydration in children has recently been stressed by Mackenzie *et al.*[9]

We therefore conducted a prospective study to assess the incidence and degree of dehydration in children with severe acute asthma who required admission to hospital, and to assess the effect of their degree of hydration on their rate of recovery while on a relatively restricted fluid intake.

Patients and methods

PATIENTS

Children aged between 5 and 12 years who attended the asthma clinic regularly and who knew how to use the Mini-Wright peak flow meter were admitted to the study if they required admission to hospital for a severe attack of acute asthma. The criterion for admission was that the peak expiratory flow rate (PEFR) remained at less than half the predicted level after two doses of nebulised salbutamol 1 ml 0·5% solution with 1 ml 0·9% saline (Ventolin).[10]

TREATMENT PROTOCOL

During the first 24 hours after admission each child received 50 ml/kg 5% dextrose/water intravenously. Oral fluids were withheld during this period, but thereafter intravenous fluids were discontinued and free oral fluids were allowed. Hydrocortisone 2 mg/kg was given intravenously every six hours for 24 hours, with prednisone 2 mg/kg/daily thereafter, reducing to their previous dose over five days. Theophylline 5 mg/kg was given orally every six hours and inhalations of nebulised 0·5% salbutamol were given every two to four hours as required. Respiratory function was monitored by daily readings of the PEFR.

ASSESSMENT OF HYDRATION

On admission the duration of the attack was recorded, as was whether the child had been vomiting before admission, and whether the child was receiving maintenance treatment with steroids or theophylline.

A clinical estimation of the state of hydration was made at the bedside, taking account of skin turgor, mucosal moistness, and eye signs. A sphygmomanometer with appropriate cuff was used to measure the difference between the inspiratory and expiratory diastolic blood pressure.

Each child was carefully weighed on admission wearing only underclothes and weighed again 24 hours, 48 hours, and seven to 10 days later. Weights were recorded by two independent observers to the nearest 10 g and the mean weight recorded. The scales were standardised at the start of the study and the same scales were used throughout the period.

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Weight at the seven to 10 day visit was assumed to represent the child's stable reference weight, and weights on admission, and 24 hours and 48 hours later, were expressed as a percentage of this.

Serum sodium and potassium concentrations (ion elective electrode, Astra 8 Beckman), serum osmolality (Micro-osmette Precision System), and packed cell volume (Coulter, Model 5+2) were measured at the same time that they were weighed. Urinary osmolality and ketones (Ames, Ketodiastix) were tested only on the first specimen of urine passed after admission.

PEFR was measured with a Mini-Wright peak flow meter on admission and after the initial inhalation of salbutamol and again whenever the child was weighed. The maximal value of three efforts was recorded.

DATA ANALYSIS

Statistical analysis was carried out by the Biostatics Unit of the South African Medical Research Council, Parowvallei.

Univariate analysis of variance (Anova) was carried out using the following variables: weight, serum sodium and potassium concentrations, osmolality, packed cell volume, and percentage of predicated peak flow, to identify the variables that changed significantly over time.

Sequential values of weight and hydration indices for each patient were compared using the paired two tailed Student's *t* test, each patient acting as his own control. Spearman correlation coefficients were calculated to work out the relationship between individual variables and the degree of dehydration. Regression analysis was also carried out on all subsets to find out which variable correlated best with the degree of dehydration.

Informed parental consent was obtained for each child studied and the protocol for the study was approved by the ethics and research committee of the Faculty of Medicine, University of Cape Town.

Results

CLINICAL EVALUATION OF THE PATIENTS

Twenty children with severe acute asthma (12 girls and eight boys, mean (SD) 9·15 (2·57), range 5–12 years) were studied. The median duration of the attack from the onset of symptoms to the time of admission was 16 hours (mean (SE) 17·7, (2·09), range 5–48). In eight the attack had lasted 12 hours or less, in 10 from 13–24 hours, and only two patients had been ill for more than 24 hours. Of the 20 children, 18 were on maintenance treatment with oral theophylline and 11 with oral steroids. Eleven children had vomited at least once.

Thirteen children were thought clinically to be about 5% dehydrated, four were thought to have borderline dehydration (2·5%), and three were considered to be normally hydrated.

DEHYDRATION AND CLINICAL AND LABORATORY MEASUREMENTS

The mean admission weight was 97·9% of stable weight ($p<0\cdot05$) (mean percentage dehydration=2·11). Using a repeated measures analysis of variance to detect an overall time effect on the variables shown in the table, significant overall changes in the serial measurements were found for weight ($p=0\cdot002$), and percentage predicted peak flow ($p=0\cdot001$).

Analysis of the significant day to day differences in the variables by Student's *t* test (also shown in the table) confirmed that a marginal increase in packed cell volume was present on admission. Despite unrestricted fluids, a small but significant fall from the 24 hour weight was recorded at 48 hours. Three children were more than 5% dehydrated by weight on admission (−5·4%, −5·7% and −6·2% of stable weight). There was no correlation between the calculated percentage dehydration and the clinical assessment (Spearman rank correlation coefficient =−0·007, $p=0\cdot98$). The degree of dehydration on admission correlated weakly with the duration of the attack. Only one of the two children whose attack exceeded 24 hours duration was dehydrated (percentage dehydration 3·3). The children who had vomited had a mean percentage dehydration of 2·2, and those with no history of vomiting had a mean % dehydration of 2·0 ($p>0\cdot8$). The only baseline measurement that came anywhere near correlating with the degree of dehydration (using Spearman rank correlation coefficients) was a fall in arterial pH ($r=0\cdot413$, $p=0\cdot07$). All subsets regression analysis of the packed cell volume, oxygen and carbon dioxide tensions, bicarbonate, pH, the difference between inspiratory and expiratory

Sequential measurements of indices of hydration expressed as mean (range)

Time from admission	*Weight (kg)*	*Percentage of stable weight*	*Packed cell volume*	*Serum potassium (mmol/l)*	*Percentage of predicted peak flow*	*Serum sodium (mmol/l)*	*Osmolality mmol/kg*
On admission	27·9 (15·3–48·6)	97·9 (93·9–101·2)	0·44 (0·35–0·63)	3·9 (2·9–5·1)	30·9 (30–49)	137·9 (131–145)	284·9 (274–292)
At 24 hours	28·0 (15·0–48·5)	98·6 (02·0–103·0)	0·41 (0·34–0·49)	3·7 (3·0–5·0)	75·3 (41–114)	137·5 (132–143)	283·9 (275–297)
At 48 hours	27·6 (15·5–47·5)	97·3 (93·2–101·2)	0·42 (0·37–0·53)	3·9 (3·5–4·6)	93·0 (50–139)	138·5 (131–147)	286·1 (277–299)
At seven to 10 days	28·5 (16·3–49·6)	100 (Reference weight	0·42 (0·36–0·47)	4·0 (3·4–4·8)	103·6 (80–139)	137·8 (133–143)	286·2 (279–306)
p Value Anova	0·0001	Not applicable	0·0784	0·1021	0·0001	0·5700	0·4227
SE of differences	0·16	Not applicable	1·16	0·12	5·15	0·73	1·59
Significant changes p <0·05 (Student's *t* test)	0 *v* 7–10 24 *v* 48 48 *v* 7–10	0 *v* 7–10 24 *v* 48 48 *v* 7–10	0 *v* 7–10 0 *v* 24	24 *v* 7–10	0 *v* 24 0 *v* 7–10 24 *v* 7–10	None	None

diastolic pressure, and percentage of predicted PEFR, confirmed that the best predictor of dehydration was a fall in pH, but the level of correlation was not sufficient for practical use (r^2=0·165, p=0·10).

CLINICAL COURSE

All 20 children had uneventful hospital stays and were discharged home several days before their seven to 10 day follow up visit. Comparison of the rate of recovery in lung function (as shown by PEFR) between the children who were below the median value of percentage dehydration (−2·3%) with those who were above the median value (by analysis of variance) showed no difference between the two groups in the rate of recovery (p=0·38).

No complications of asthma were encountered, and all patients were clinically well with normal PEFR at the seven to 10 day follow up study.

Discussion

Few controlled studies have investigated the incidence and treatment of dehydration in severe acute asthma.[10–12] None of these studies have assessed the degree of dehydration normally encountered in children with severe acute asthma, or the effect of a relatively restricted fluid regimen on the rate of recovery from the attack.

In this prospective study, by serially measuring clinical and laboratory indices of hydration normally available to the clinician, we found that a mild degree of dehydration was common among children presenting with severe acute asthma. Within the range of dehydration encountered the degree of dehydration on admission bore no relation to the rate of recovery when children were treated on a relatively restricted fluid intake. Our results therefore support the argument that additional fluids above baseline requirements are unnecessary in severe acute asthmatic attacks.

Three lines of evidence support a conclusion that the children that we studied had only mild dehydration. The first, obtained by comparison of the admission weight with the seven to 10 day reference weight (baseline), showed that the mean (SD) percentage dehydration was 2·1 (2·3), range 1·6 to 6·2, median 2·3. Secondly, normal serum electrolyte concentrations and osmolality were recorded on admission and throughout the seven to 10 day observation period, and the mean packed cell volume on admission was mildly but appreciably raised. Thirdly, there was no significant weight gain once the children were allowed unrestricted fluids orally after the initial 24 hour period when fluids were restricted to 50 ml/kg/24 hours. This supports our conclusion that none of them had unrecognised significant dehydration on admission.

In our interpretation of the serial weight changes we have assumed that the weight of a child seven days after a severe acute attack who has recovered completely represents a stable baseline reference weight. We have also assumed that rapid fluctuations in weight reflect fluid balance. These assumptions are reasonable, given the fact that it is practically impossible to obtain a child's reliable weight as a reference scale immediately before the onset of the acute attack of asthma. It has previously been shown that in the short term respiratory tract illnesses (for example, pneumonia and otitis media) cause no discernable retardation in the growth rate of most well nourished children.[13]

The possibility that treatment with steroids could have influenced the seven to 10 day baseline assessments must be considered. Short term weight increases associated with treatment with steroids are usually attributable to mineralocorticoid effects and some children do gain weight quite quickly on high doses of steroids. We do not consider that in our patients steroids caused any appreciable increases in weight, because in the first instance we noted a decrease in mean weight ($p<0·05$) at 48 hours (table), the point at which the patients had received their highest doses of their tailing courses of prednisone. Secondly, serial monitoring of the serum sodium and potassium concentrations and osmolality (table) provided no evidence supporting mineralocorticoid activity at any of the assessments. Thirdly, we discontinued the short course of prednisone on day 5, at least 48 hours before the seven to 10 day assessments of weight. In view of the short reported serum half life of prednisone (3·6 hours) any pharmacological effects of prednisone at the seven to 10 day assessments were likely to be minimal.[14]

If, however, we accept that treatment with steroids may have increased the weight in our patients, we have overassessed the degree of dehydration and the mean percenage dehydration on admission is even less than the 2·1 that we found. This would strengthen our conclusion that dehydration in severe acute asthma is usually mild. To our knowledge there are no published data on the effects of tailing off doses of prednisone on weight in the presence of mild dehydration. Our data provide reasonable evidence that any weight gain caused by the steroids in acute childhood asthma is likely to be minimal.

Factors that are likely to influence the degree of dehydration encountered during an acute asthmatic attack include the duration of the attack, ambient temperature, maintenance drug treatment (for example, steroids and theophylline), the presence of fever, oral fluid intake before and during the attack, and vomiting. Several of these factors may occur in varying degrees in a given patient and some factors may compensate for others. We found that children with a history of vomiting were not significantly more dehydrated than those who had not vomited. The clinician overestimated the degree of dehydration in 13 of 20 cases. Mouth breathing by a distressed child causes drying of the buccal mucosa and can falsely suggest dehydration to the attending clinician. In this study the degree of dehydration correlated weakly with the duration of the attack. This finding suggests that most children with acute asthma maintain hydration where possible by continuing to take oral fluids. The severity of the attack as measured by the difference between inspiratory and expiratory diastolic pressure, and oxygen and carbon dioxide tensions, did not correlate with the degree of dehydration. A mild compensated metabolic acidosis (as shown by a fall in pH) did, however, correlate more strongly with a state of mild dehydration than changes in any of the other variables measured by multiple regression analysis.

To assess the effect of the degree of dehydration on the rate of recovery of the PEFR, the recovery of children who were more dehydrated was compared with those who were less dehydrated. A greater degree of dehydration on admission did not impair the rate of recovery, and as all the children received the same fluid regimen, it suggests that additional fluids are not required to assist airway recovery. Supporting this observation, Nadel emphasised that there have been no studies to support the assumption that fluids will reduce the viscosity of tenacious secretions or influence the mechanisms that could be expected to assist their removal from the airways.[15]

In animal experiments, Marchette *et al* found that in allergic sheep with antigen induced bronchial obstruction, tracheal mucus velocity, (as an index of lower airway mucociliary clearance) was impaired by 5% dextrose infusions of 25–35 ml/kg, although no impairment was observed in normal sheep.[16] This raises further questions concerning the possible deleterious effects of too much fluid on children with severe acute asthma.

Baker *et al* studied the weights of asthmatic patients and warned about the dangers of overhydration and the possibility of water intoxication.[7] In their study of seven patients (age range 7–52 years) concentrations of antidiuretic hormone were raised in all patients and serum osmolality was decreased. Dawson *et al* measured the concentrations of antidiuretic hormone in the plasma of 10 asthmatic children and found that they were appreciably increased.

If concentrations of antidiuretic hormone are inappropriately raised, abundant oral and parenteral fluids may aggravate mucosal oedema of the airways.[10] This will cause further airway narrowing, perhaps premature airway closure, and worsening of the asthmatic attack. On the other hand Bahna and Kaushik could find no evidence of the syndrome of inappropriately raised antidiuretic hormone secretion in 26 children with acute severe asthma.[12] Singleton *et al* have, none the less, shown that children with severe acute asthma have impaired water excretion after water loading and are at risk of hyponatremia if given hypotonic fluids for a prolonged period of time.[11] We believe that the most likely explanation for the raised concentrations of antidiuretic hormone that have been reported in severe acute asthma is the presence of mild dehydration.

Straub *et al* reported haemoconcentration in nine adult patients with asthma using erythrocytes labelled with ^{51}Cr and a slight increase in packed cell volume in 13 of 20 patients with severe attacks, but this did not correlate with their assessments of dehydration using serial measurements of weight. Our study also showed a slight, but significant, increase in the packed cell volumes of children presenting with severe acute asthma.

Taken collectively these studies support our conclusion that additional fluids should be given with caution to a child with severe acute asthma. As concentrations of antidiuretic hormone are increased in acute childhood asthma, we believe that the most likely explanation is that this is an appropriate response to mild dehydration rather than a syndrome of inappropriate section of antidiuretic hormone. Until there is evidence that the liberal giving of fluids has a beneficial effect on the course of the disease, or that withholding fluids to achieve a state of mild dehydration is beneficial, it seems prudent to aim for a state of normal fluid balance in children with severe acute asthma. When fluids cannot be taken orally, calculation of the maintenance volume of low solute intravenous fluid should be based on about twice the estimated insensible loss—that is, roughly 50 ml/kg/24 hours. This is a safe and appropriate volume, is not accompanied by significant electrolyte changes or fluid retention, and is consistent with rapid recovery in the PEFR.

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Body water measurement in growth disorders: a comparison of bioelectrical impedance and skinfold thickness techniques with isotope dilution

J W Gregory, S A Greene, C M Scrimgeour, M J Rennie

Abstract
Total body water was estimated as part of the assessment of body composition in children with growth disorders, using the newly commercially available method of bioelectrical impedance. This was undertaken to compare the precision and accuracy of the results with those derived from skinfold thickness against measurement of stable isotopically labelled water ($H_2{}^{18}O$) dilution as a standard. The comparisons were carried out to see to what extent the impedance method could be applied with confidence to assessment of children with growth disorders. Total body water was derived from impedance (I) using an association with height (Ht^2/I). Impedance and skinfold thickness estimates of total body water were equally precise when compared with values obtained from $H_2{}^{18}O$ dilution (limits of agreement $-1{\cdot}9$ to $+1{\cdot}3$ and $-1{\cdot}7$ to $+2{\cdot}0$ kg respectively). The mean intraobserver coefficient of variation for repeat measurements of impedance was 0·9% compared with 4·6% for skinfold thickness with an interobserver coefficient of variation for impedance of 2·8%. Bioelectrical impedance estimation of body composition is likely to be of value in the growth clinic when expertise in measurement of skinfold thickness is limited or repeated measurements are to be undertaken by different observers.

Body composition measurement is useful in the diagnosis of pathology, assessment of disease progress and response to treatment. Techniques currently in use are mostly indirect, often expensive, difficult, and time consuming. Furthermore, the original reference data for body composition was based on the chemical analysis of the cadavers of six adults, several of whom died of illnesses likely to make their body composition unrepresentative.[1] Values for body composition of children have often been derived by extrapolation from those values together with those obtained from the chemical analysis of a 4·5 year old boy and newborn infants.[2]

Densitometric analysis of body fat content by the underwater weighing technique is not widely applicable in the clinical context and is based on uncheckable assumptions concerning the density of fat and lean tissues. Skinfold thickness measurement is a standard method of body composition assessment in clinical paediatric practice. Regression equations derived from underwater weighing[3] and deuterium oxide dilution[4] methods for the calculation of body density and thus body fat[5] from the sum of four skinfold thicknesses have been published for use in adolescents[3] and prepubertal children.[4] The method of skinfold thicknesses may, however, be unreliable because distribution of fat within the body may vary with sex, age, and race.[1] There is considerable variability between measurements made by different observers on the same individual and the technique requires practice to reduce the error to the minimum possible with a single observer.

The present 'gold standard' for body water measurement from which body composition may be estimated depends on the dilution of isotopically labelled water tracer. This assumes that the tracer is uniformly distributed throughout the body water compartments and excreted like native water. Tritium is radioactive and thus ethically unacceptable for use in children but both deuterium (^2H) and ^{18}O are stable isotopes that may be used as tracers of water without radiation hazard. $H_2{}^{18}O$ is expensive and in short supply but the $H_2{}^{18}O$ dilution space is a more accurate measure of total body water, usually about 3% less than the ^2H_2O space[6] because of greater exchange of ^2H with non-aqueous components. However, isotopic analysis of ^{18}O requires expensive mass spectrometric facilities and expertise in their use.

The measurement of impedance is a technique for the indirect estimation of total body water and has recently been evaluated in several clinical situations. It is based on the association between the physical dimensions and electrical properties of a conductor. The impedance to the passage of a current through a conductor varies directly with the product of its volume resistivity and the length squared and inversely with its volume. Hoffer *et al* have confirmed that in the human body, assuming water to be the electrical conductor, total body water is related closely to height^2/impedance (Ht^2/I).[7] The technique has been validated in adults,[8–10] but there is little information on its use in children. Given that the technique is quick, safe, and non-invasive, it should be of particular value in the assessment of body composition in children.

We have therefore undertaken a preliminary study in children with growth disorders to assess how well bioelectrical impedance predicts total body water determined by $H_2{}^{18}O$ dilution in those circumstances. We have compared the results with those from measurements of skinfold thickness to identify the relative utility of each of the simple indirect methods.

Patients and methods

Thirty four children (28 boys, six girls) under-

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Table 1 Details of patients and measurements

	Mean (SD)	*Range*
Age (years)	12·0 (2·5)	7·4 to 15·7
Height (cm)	132·4 (13·6)	106·5 to 151·7
Height SDS	−2·56 (1·08)	−4·60 to 1·06
Weight (kg)	29·9 (8·1)	15·7 to 49·8
Total body water ($H_2{}^{18}O$ dilution) (kg)	17·3 (4·3)	9·3 to 25·1
Total skinfolds (mm)	33·5 (16·0)	17·0 to 78·0
Resistance (ohms)	608 (71)	489 to 742

SDS=growth measurement expressed as standard deviation score for chronological age.[19]

going investigation of growth disorders were assessed. Of these, 19 had constitutionally delayed puberty (height <3rd centile, bone age delay >1·5 years), nine had growth hormone deficiency (growth hormone <10 μg/l in response to a standard insulin stress test,[11] and six had normal variant short stature (height <3rd centile, growth hormone >10 μg/l in response to a standard insulin stress test). Details of the subjects are shown in table 1 and these children are representative of the referral pattern to our clinic. Height was measured using a Holtain stadiometer and weight with a beam balance.

Total body water was measured from $H_2{}^{18}O$ dilution after giving 0·3 g $H_2{}^{18}O$/kg estimated total body water by mouth after an overnight fast (^{18}O was 10·4 atom % from Isotec Inc). Urine specimens for analysis were taken before and five hours after the dose. Urine aliquots of 400 μl were equilibrated with 5% carbon dioxide in 20 ml Vacutainers (Becton Dickinson) for three days before analysis of the carbon dioxide for $^{18:16}O$ ratio using a Finnigan MAT Delta D gas isotope ratio mass spectrometer fitted with an automated breath gas analysis system.[12] Standard corrections for fractionation and dilution of the label by the added carbon dioxide were applied.[13] Total body water was calculated by the method of Schoeller *et al* after standardising the enrichment of the given tracer by analysis of suitable dilutions with tap water.[6]

Bioelectrical impedance measurements were made using Holtain body composition analyser (Holtain Limited). The technique is simple to perform and highly acceptable to patients. Electrodes are applied for a few seconds to the dorsum of the right wrist and to the flexor surface of the right ankle through which a harmless 800 μA, 50 khz high frequency alternating current is passed allowing the impedance to be measured.

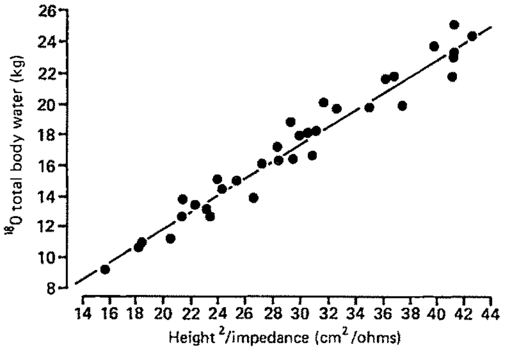
Skinfold measurements were made by a single observer (JWG) using a Holtain skinfold caliper from the triceps, biceps, subscapular, and suprailiac sites as described previously.[3] Separate regression equations were used for converting the sum of the four skinfold thicknesses into body density for prepubertal[4] and adolescent[3] children. Fat mass was calculated[5] and for comparative purposes total body water was deduced (assuming that fat mass is anhydrous and fat free mass contains 730 g water/kg weight[14]) using the equation, total body water= 0·73×(weight−fat mass).

Comparison of the values for total body water obtained from impedance and skinfold techniques with those obtained by isotope dilution were made using the method of Bland and Altman.[15] This entails comparing the difference between the methods against the mean of the two methods, with results expressed as the bias (mean of the differences) together with its limits of agreement (mean (2 SD) difference) and the 95% confidence intervals for the lower and upper limits.

Results

Subject details and measurements by each technique are shown in table 1. The association for Ht^2/I and total body water derived from $H_2{}^{18}O$ dilution produced the regression equation: total body water=0·79+0·55 (Ht^2/I) (figure). Statistical analysis of the variance involved in prediction of total body water by values derived from impedance and skinfold thickness measurements suggests both methods are of similar precision when compared with the $H_2{}^{18}O$ dilution method (table 2).[15]

Repeated measurements of impedance by the same observer at the same time of day resulted in a mean coefficient of variation for the measurement of 0·9%. When repeat measurements were made at different times throughout the day regardless of mealtimes or a full bladder, the coefficient of variation only increased to 2·4%. Repeat measurements on the same occasion by different observers resulted in a coefficient of



The association between height²/impedance (Ht^2/I) and total body water measured by $H_2{}^{18}O$ dilution. Total body water=0·79+0·55 (Ht^2/I).

Table 2 Total body water (kg) derived from $H_2{}^{18}O$ dilution compared with that from skinfold thickness and impedance (Ht^2/I)

	Skinfold thickness	*Ht^2/I (this study)*	*Ht^2/I (Davies et al[18])*
r	0·98	0·98	0·98
Bias	−0·3	0·1	−0·1
Limits of agreement	−1·9 to 1·3	−1·7 to 2·0	−2·0 to 1·9
95% Confidence interval:			
Lower limit	−2·4 to −1·4	−2·3 to −1·2	−2·6 to −1·4
Upper limit	0·8 to 1·8	1·4 to 2·5	1·3 to 2·5

variation of 2·8%. In contrast, the coefficient of variation for repeat skinfold measurements taken by a single experienced observer was 4·6%.

The application of skin electrodes in the use of the impedance technique was perceived as less threatening and thus better tolerated than the use of skinfold calipers in children under the age of 8 and in our experience may be used without difficulty in children as young as 3 years old (unpublished data).

Discussion

The principles of bioelectrical impedance were described nearly 30 years ago,[16 17] but only in the last five years have instruments suitable for clinical measurement become available. Our study confirms the results of Davies *et al* who derived total body water from impedance in 26 children and adolescents with a variety of disorders (inflammatory bowel disease, growth hormone deficiency, diabetes, and obesity).[18] We found a mathematical association very similar to their findings (total body water$=-0{\cdot}5+0{\cdot}6\times \mathrm{Ht}^2/\mathrm{I}$). The study of Davies *et al* involved children with a variety of illnesses and it is reassuring that in our own study, focusing on children with growth disorders in whom fat content may be abnormal, that the above association holds. Together these results suggest that impedance may be reliably used for the assessment of body composition in paediatric practice, although clearly much larger studies are necessary to confirm the precision of the technique in girls and in disorders other than those affecting growth.

Our results (table 2) comparing both impedance and the established technique of skinfold thickness estimation with $H_2{}^{18}O$ dilution show concordance of estimates of the bias and extent of agreement of the indirect methods in predicting total body water, although the confidence intervals for the limits of agreement are wide, reflecting the small size of our sample and the inherent imprecision of indirect measurements of total body water. The concordance holds even when estimates of total body water based only on published equations are compared.[3 4 18] This avoids the minimisation of prediction error that is introduced when our equation for deriving total body water from impedance is compared with total body water derived from isotope dilution, the former having previously been derived from the latter. Impedance and skinfold techniques, when used by a single experienced observer, are of comparable precision in the assessment of total body water, though the coefficient of variation for repeat measurements by the former method is considerably less.

In summary, bioelectrical impedance appears to be at least as accurate and precise a method for the measurement of total body water as the skinfold thickness technique performed by a single experienced observer. The impedance method is of advantage with younger children or when the clinician has limited expertise in skinfold measurement. It is also of value when different observers are undertaking serial measurements; this is because of the smaller variation in values obtained by one or more than one observer and so is the preferred choice when monitoring patients' response to treatment.

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Raised urinary secretory IgA in chronic diarrhoea

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Abstract

Secretory IgA outputs in urine have been measured in 24 malnourished Gambian children who had been admitted to hospital with chronic diarrhoea and in 43 children from a rural Gambian village. Village children of poor nutritional state (≤74% weight for age compared with the National Center for Health Statistics reference curve) had secretory IgA outputs that were only one third of those of better nourished individuals. In contrast, the patients with chronic diarrhoea had secretory IgA outputs that were significantly raised compared with village children, regardless of nutritional state. These results demonstrate that secretory IgA production in the urinary tract can be stimulated by intestinal disease, suggesting that malnourished children are able to mount a response to mucosal infection and supporting the hypothesis of a common secretory immune system.

Secretory IgA, the principal immunoglobulin of mucosal defence in the human, is found in substantial quantities in most external fluids. Secretory IgA concentrations in the secretions of the eye, nasopharynx, mouth, and duodenum have been shown to be significantly reduced in children with moderate and severe malnutrition.[1–6] An appreciable decrease in IgA containing cells has been noted in jejunal mucosae of severely malnourished children.[7] These studies suggest that mucosal defence is compromised by malnutrition and that this may be a contributory factor in the high incidence of infection common in malnourished children. Intestinal lymphocytes from malnourished children, however, have been shown to have enhanced abilities to synthesise secretory IgA in vitro.[8] Raised concentrations of secretory IgA have been observed in the duodenal fluid of malnourished children with concomitant enteric infection.[9] This suggests that the capacity to increase secretory IgA production in response to local infection may be retained in malnutrition.

The study of Gambian children, reported here, extends these findings by demonstrating that secretory IgA production into urine is lower in malnourished children but that it is raised in those with chronic diarrhoea. This observation indicates that malnourished children are able to mount a mucosal immune response to infection. In addition, it suggests that secretory IgA production at one location can be stimulated in response to infection at another mucosal site, lending support to the concept of a common secretory immune system.

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Subjects and methods

SUBJECTS

Twenty four children (11 boys and 13 girls) who had been admitted with malnutrition and chronic diarrhoea (three or more loose stools/day for at least two weeks) to the children's ward of the Medical Research Council (MRC) Laboratories, Fajara, The Gambia, West Africa, were recruited into the study. The children were 10–31 months' old and had been suffering from diarrhoea for a median duration of 14 weeks (range 2–52). Twenty three of the 24 patients had weight for height relative to the National Center for Health Statistics (NCHS) reference[10] of less than ≤74%; seven children had marasmic kwashiorkor and one kwashiorkor. The mean (SD) weight for age of these patients was 58 (6)% (range 49–73). One patient was undernourished with a weight for age of 87% and weight for height 88%. Microscopy of stools and small bowel mucosae together with serological tests showed that 15 patients were infected with *Giardia lamblia*, two of whom also had *Strongyloides stercoralis* infection, and two patients were infected with *Ascaris lumbricoides*.

Two urine collections were made, the first at the beginning of the study (week 1), the second three to four weeks later immediately before discharge (week 3). Microbiological analysis of urine collected at the beginning of the study showed that one patient had a klebsiella urinary tract infection, 18 had sterile urine, and five were untested. Blood from each patient was collected at week 1 and analysed for serum IgA using an automated turbometric technique on a centrifugal analyser (Cobas-Bio, Roche).

To assess urinary IgA production in Gambian children without chronic diarrhoea, urine samples were collected from 43 boys aged 9–25 months who were living in the rural villages of Keneba and Manduar during November and December 1987. The children had a mean (SD) weight for age of 80 (12)% (range 55–121) and a mean (SD) weight for height of 87 (7)% (range 75–108). For data analysis the group was divided into quartiles by weight; the most poorly nourished group having weight for age ≤74% (n=11).

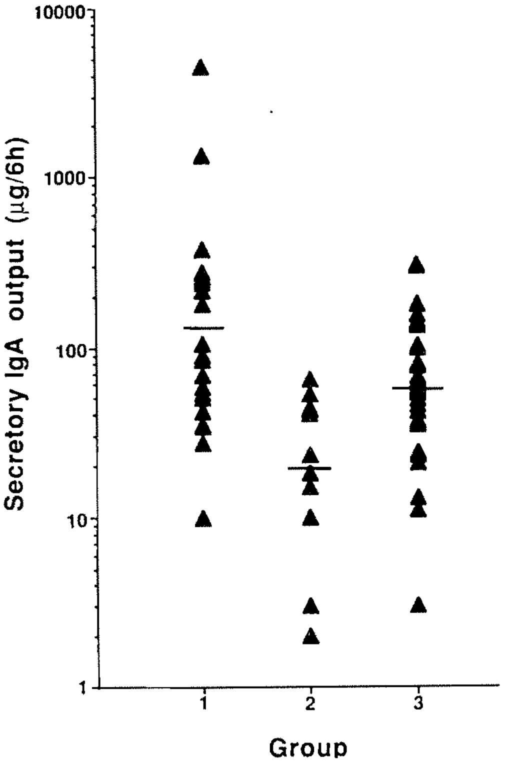
The urine samples were collected as part of studies on intestinal function which had been approved by the MRC Gambia ethical committee.

URINE COLLECTION AND ANALYSIS

Urine samples in both groups of children were collected over a timed period of five to six hours using disposable, self adhesive urine bags (Hollister) to which one drop of 0·2 g/ml chlorhexidine gluconate had been added as preservative. At the end of the collection period, the volume of urine passed was recorded and samples were stored at −20°C.

Aliquots of urine samples were diluted 10–80 times and analysed for IgA using two enzyme linked immunosorbent assay (ELISA) methods. One method is specific for molecules containing both α chain and secretory component determinants (secretory IgA) and the other detects any molecule containing α chain determinants (secretory IgA, serum IgA, IgA fragments).[11] Purified human secretory IgA (Sigma) was used as standard. When secretory IgA is the only IgA species present the ratio of results obtained with the two methods (total IgA: secretory IgA) is unity. Between batch precision, measured using a pooled diluted breast milk sample analysed on each plate during the series, was 5% for both assays. The lower limit of measurement of IgA in urine was 30 µg/l. Creatinine was measured in urine diluted 1:10 with 0·1 mmol/l hydrochloric acid using the Jaffe method on a centrifugal analyser (Cobas-Bio, Roche).

There was no evidence of any age trends in the data set and consequently the results from all subjects within each group have been analysed together. Similarly, within the group of patients with diarrhoea, no significant differences were observed between boys and girls and the results for both sexes have been combined. The data were transformed to logarithms to normalise positively skewed distributions. Urine volumes, secretory IgA outputs and creatinine outputs were standardised to amount produced per six hours. Student's *t* test for independent samples was used to compare groups, paired *t* test to compare the urines of patients collected at weeks 1 and 3. Geometric means (antilog (mean of logged values)) and, as a measure of variance, a value termed the geometric standard error (defined as [antilog(mean+standard error of logged values)–geometric mean]) are reported.



Urinary secretory IgA output of Gambian children. The groups of children are as follows: (1) malnourished with chronic diarrhoea, n=24, (2) controls without diarrhoea, weight for age ≤74%, n=11, (3) controls without diarrhoea, weight for age ≥75%, n=32. The horizontal bar across each group denotes the geometric mean.

Results

The results of the urine analyses are given in the table. For the subjects living in the rural community, secretory IgA outputs were significantly lower, by a factor of three ($p<0\cdot01$), in the children with weight for age ≤74% compared with those who were better nourished. No further effect of anthropometric status was visible in the children with weight for age ≥75%. In contrast, the secretory IgA outputs of the patients with chronic diarrhoea were significantly raised compared with the village children. The difference in mean IgA outputs was considerable: 6·8 times higher than the outputs of poorly nourished children ($p<0\cdot001$) and 2·3 times higher than well nourished children ($p<0\cdot01$). In the children with chronic diarrhoea, the higher outputs of secretory IgA were not related to anthropometric status and were still observed in those patients with severe malnutrition (geometric mean (+SE) secretory IgA output (µg/6h): weight for age ≤59%=127 (+33), n=12; weight for age ≥60%=120 (+75), n=12). These findings persisted when only the boys in the group with chronic diarrhoea were compared with the village boys (boys with

Secretory IgA and creatinine in the urine of Gambian children with and without chronic diarrhoea

	Diarrhoea	*Control*	
		≤74% *Weight for age*	≥75% *Weight for age*
Secretory IgA output (µg/6h)	123 (+37)	18 (+8)*§	54 (+10)†
Creatinine output (mg/6h)	15 (+2)	13 (+2)‖	19 (+2)
Secretory IgA concentration (µg/l)	1340 (+426)	433 (+190)‡	615 (+130)‡
Creatinine concentration (mg/l)	163 (+28)	295 (+72)‡	252 (+33)‡
Volume (ml/6h)	95 (+15)	43 (+13)†	71 (+11)
Secretory IgA:creatinine (µg/mg)	8·2 (+2·5)	1·5 (+0·6)*‖	2·9 (+0·5)*
Total IgA: secretory IgA (µg:µg)	1·3 (+0·1)	1·4 (+0·2)	1·2 (+0·1)
No of children	24	11	32

Values are geometric mean (+geometric standard error) as defined in methods section. Control subjects are divided by weight for age relative to the NCHS reference.
Significance of *t* test comparing diarrhoea and control children: *$p<0\cdot001$, †$p<0\cdot01$, ‡$p<0\cdot05$.
Significance of *t* test comparing control children with weight for age ≤74% and ≥75%: §$p<0\cdot01$, ‖$p<0\cdot05$.

diarrhoea, secretory IgA output (μg/6h): 91 (+32), n=11). No correlations were observed between secretory IgA output and weight for height in any group of children.

The raised secretory IgA outputs of the children with chronic diarrhoea were reflected in increased urinary concentrations of secretory IgA and secretory IgA: creatinine ratios (table). The ratio of total IgA: secretory IgA in the urines of both groups was similar at around 1·3, demonstrating that the majority of urinary IgA was in the secretory form, and that the proportion of species other than secretory IgA (fragments, serum IgA) were comparable in all groups. The similarities in total:secretory ratios and creatinine outputs between the patients and village children indicate that the observed differences between groups were unlikely to be artefacts caused by potential variations in the completeness of urine collections or in sample preservation.

No significant differences were observed in any parameter measured in the urines of the chronic diarrhoea patients at week 1 and week 3. The changes in values measured for each individual were not related to their clinical progress during the three week interval. No associations within this group were observed with anthropometric state or the presence of enteric parasites. The one subject with a urinary tract infection had secretory IgA outputs in the middle of the group range. No significant differences were noted in any parameter between boys and girls. The geometric mean (+SE) serum IgA concentration of the diarrhoea patients was 14·1 (+4·5) mg/l. No correlations were found between serum IgA concentrations and either urinary IgA concentrations or outputs at week 1.

Discussion

This study has demonstrated that poorly nourished children living in rural West Africa have outputs of secretory IgA in their urine that are approximately one third of those of better nourished individuals. This finding is in agreement with reports from Thailand, India, and South America in which reductions of 35–50% have been noted in the secretory IgA concentrations of tears, saliva, nasopharyngeal fluid, and duodenal juice during moderate and severe malnutrition.[1–6] This study has also demonstrated, however, that malnourished children who are suffering from chronic diarrhoea have raised outputs of secretory IgA in their urine. Although previous studies have suggested that mucosal infection can stimulate local secretory IgA production in malnourished children,[9] this is the first report to suggest that infection of the gastrointestinal tract can elicit a response in the output of urinary IgA.

Secretory IgA is a large protein with a molecular weight of approximately 375 000 daltons. It is composed of dimeric IgA, produced by B lymphocytes resident in mucosal lymphoid tissue, which is coupled with a polypeptide, secretory component, in the local epithelial cells before secretion. In contrast, the IgA that circulates in blood is predominantly in a monomeric form with a small proportion present in polymers and complexes; none of these species contains secretory component. The use of two sensitive ELISA methods in the present study, one specific for secretory IgA, the other for any molecule containing regions recognisable by anti-IgA antibodies (secretory IgA, serum IgA, IgA fragments); established that the majority of IgA in the urine of Gambian children was secretory IgA and that it was the output of this molecule that was affected by malnutrition and infection. The observed rise in urinary IgA output during chronic diarrhoea cannot, therefore, be ascribed to an influx of small IgA species from the circulation. This view is further supported by the lack of any association between urinary IgA and serum IgA concentrations in the patients with chronic diarrhoea.

As the molecular size of secretory IgA is considerably above the upper limit for filtration through the kidneys, it is highly unlikely that secretory IgA in urine originates at a distant site and is transported into urine via the circulation. It is more probable that the secretory IgA is produced locally in the mucosal epithelium of the urinary tract. The low urinary IgA outputs of poorly nourished Gambian children noted in this study may have been the result of a reduction in the density of resident B lymphocytes as has been described in the gastrointestinal tract.[7] An increase in the population of these lymphocytes or stimulation of secretory IgA secretion could account for the observed rise in urinary IgA outputs by Gambian children with chronic diarrhoea.

The mechanism by which infection in the gastrointestinal tract could result in increased urinary IgA production is unknown. It is possible that lymphocytes from the lymphoid tissue of the gut could migrate through the lymphatic system to the urinary tract. This trafficking of lymphocytes between mucosal sites has been hypothesised to be responsible for the range of specificities observed in breast milk secretory IgA.[12] Alternatively, it is possible that some factor may be released into the circulation in response to the enteropathy that stimulates secretory IgA production in the urinary tract. This factor might possibly be a lymphokine released from activated T cells within the small intestinal mucosae. This same group of children was shown to have jejunal changes consistent with a cell mediated immune reaction to luminal antigens.[13] A factor with the ability to stimulate the differentiation of lymphocytes into IgA producing cells has been demonstrated in breast milk.[14] Whatever the mechanism involved, the results of this study indicate that there is communication between different secretory tissues of the body, a finding that is consistent with the hypothesis of a common secretory immune system.[15 16] They also demonstrate that, despite the reduction in secretory IgA production which accompanies poor nutritional state, malnourished children retain the capacity to mount a mucosal response to infection.

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The *BMJ* and quack medicines

Sir William Osler considered the urge to take medicines to be one of the characteristics that define the human race. Useless cures have no doubt always been advocated, and not only by unqualified practitioners, and large fortunes have been made by the sellers of proprietory medicines of secret formula. In the September issue of *History Today* (1990;**40**:45–51) Peter Bartrip describes the heyday of patent medicines in the nineteenth and early twentieth centuries and the part taken by the *BMJ* in their control. Under two editors, Ernest Hart (1867–1898) and Dawson Williams (1898–1928) the journal mounted a campaign against proprietory medicines and Williams published analyses of various popular cures showing them to be made up of ingredients that were worthless in both a medical and a monetary sense. Publication of the exposés began in 1904 and a book, *Secret Remedies. What They Cost and What They Contain*, published in 1909 was a bestseller and followed two years later by *More Secret Remedies*. Largely as a result of the journal's campaigning, a parlimentary select committee was appointed 1912 to look into the problem and its report called for strict controls on the manufacture and advertising of patent medicines. Unfortunately the report was published in 1914 on the day the first world war began and the recommendations were ignored. Legislation in 1917, 1939, and 1941 prohibited advertising of cures for venereal diseases, cancer, and a variety of other conditions.

Despite its campaigning the *BMJ* continued, for financial reasons, to carry advertising for medicines of undisclosed composition and it was strongly criticised for doing so by the editor of the *Journal of the American Medical Association* in 1912 and by the Canadian Medical Association in 1924. Tobacco advertising caused a problem in the 1950s and was finally refused in 1957.

Peter Bartrip's book, *Mirror of Medicine. A History of the British Medical Journal*, was published by Oxford University Press on September 27th.

ARCHIVIST

Handwashing and cohorting in prevention of hospital acquired infections with respiratory syncytial virus

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Abstract

Hospital acquired infections with respiratory syncytial virus are a major problem. The virus is spread predominantly by infected nasal secretions and we investigated whether we could reduce its incidence by cohorting babies on each ward into designated areas and encouraging staff and parents to wash their hands.

We examined the incidence of hospital acquired infection due to respiratory syncytial virus in all children <2 years old and in those with congenital heart disease. In 1986–7, before any intervention, 18 (4·2%) of 425 hospitalised children <2 years old developed hospital acquired infection due to respiratory syncytial virus. In 1987–8, after intervention, five (0·6%) of 840 children developed hospital acquired infection but there were fewer ward admissions with community acquired infections due to the virus. In 1988–9, when there were more community acquired infections than 1986–7, six (1·1%) of 552 children developed hospital acquired infection. In 1986–7, eight (34·8%) of 23 children <2 years old with congenital heart disease developed hospital acquired infection due to respiratory syncytial virus; all eight were among 11 children with congenital heart disease hospitalised for more than 14 days. In 1987–8, one (3·3%) of 30 children with congenital heart disease developed hospital acquired infection due to respiratory syncytial virus and in 1988–9 there was one (2·1%) case out of 47 children with congenital heart disease.

Handwashing and cohorting significantly reduce the incidence of nosocomial respiratory syncytial virus infection.

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Respiratory syncytial virus is a major cause of morbidity and mortality in children world wide.[1] Children's services in hospital present a particular problem as not only are large numbers of infants admitted from the community each year with bronchiolitis and other infections caused by respiratory syncytial virus but there is a subpopulation of hospitalised children who are at relatively high risk from infection. Children at increased risk from respiratory syncytial virus infection include those with congenital heart disease, particularly if they have pulmonary hypertension,[2] babies who are born preterm and have chronic lung disease such as bronchopulmonary dysplasia,[2] immunocompromised children,[3] and those with cystic fibrosis.[4]

Respiratory syncytial virus spreads readily within hospitals to infect children and staff.[5] Gloves and gowns[6] and even goggles[7] have been found by some authors to be of value in decreasing the incidence of hospital acquired (nosocomial) infections but others have been unconvinced by the efficacy of gowns and masks.[8] It is now widely accepted in neonatal units that handwashing is an important way of preventing nosocomial infections, but this has been less firmly emphasised on general paediatric wards, at least in the United Kingdom, and its efficacy in preventing respiratory syncytial virus infection has not been evaluated. In an effort to decrease the incidence of nosocomial respiratory syncytial virus infections we introduced cohorting of babies with suspected or proved respiratory syncytial virus infection and mounted an educational programme to emphasise the importance of handwashing to staff and relatives.

Patients and methods

In order to assess the importance of nosocomial respiratory syncytial virus infection we retrospectively collected data on all children with respiratory syncytial virus infection on any of the paediatric medical wards in the winter of 1986–7. Infection by the virus was diagnosed by indirect immunofluorescence on nasopharyngeal secretions using a bovine antiserum against respiratory syncytial virus (Central Public Health Laboratory, Colindale) and a fluorescein conjugated antibovine antiserum (Wellcome) and/or by culture of secretions on MRC-5 fibroblasts and HeLa cells.

In order to define a population at risk of developing respiratory syncytial virus infection we determined the number of children under 2 years of age hospitalised on the two paediatric medical wards (one 17 and one 19 bed) and the (six bed) paediatric intensive care unit and the number of days they spent in hospital. Each medical ward contained six single rooms. To examine a group at high risk for severe respiratory syncytial virus infection the records were reviewed of all children under 2 years of age with congenital heart disease admitted to the paediatric medical wards over the period of the 1986–7 outbreak, from the first reported case until the last case had been discharged or was no longer infectious. In our hospital cardiac patients are admitted onto one of the general paediatric medical wards. Cases were classified as having either community acquired infection if they were admitted with a respiratory illness and had not been in hospital in the 10 days before developing symptoms or hospital acquired infection if they had previously been in this hospital in the preceding 10 days. All children with hospital acquired infection had in fact previously been in this hospital within five days of developing symptoms; that is the average incubation period of infection with the virus.[6] Follow up after discharge to identify late onset hospital acquired infection was not routinely performed. Children who acquired their respiratory syncytial virus infection at another hospital were considered to have community acquired infections for the purpose of this study. Children, not previously hospitalised, admitted with a non-respiratory condition but developing a respiratory illness due to respiratory syncytial virus within five days of admission were deemed to have community acquired infection, although no such cases actually occurred in the study period. Children were defined as having recurrences of infection with the virus if their symptoms recurred more than 30 days after their initial infection and respiratory syncytial virus could again be isolated.

The severity of the infection, both hospital and community acquired, was assessed using a clinical grading.[9] Grade 1: children tolerated oral feeds, grade 2: required nasogastric tube feeds, grade 3: required nasogastric tube feeds and supplemental oxygen, grade 4: required intravenous fluids and supplemental oxygen, and grade 5: required artificial ventilation.

For the next two winters (1987–8 and 1988–9) the same data were prospectively collected. In addition some interventions were made to try to reduce the incidence of hospital acquired respiratory syncytial virus infection. Because the medical wards alternate in taking emergency admissions it was not practicable to have a ward dedicated to children with the infection. A six bedded area in each of the two paediatric medical wards including two single rooms was, therefore, cordoned off by screens and designated the 'respiratory syncytial virus area'. Children admitted with suspected respiratory syncytial virus infection were nursed in this area until the result of an indirect immunofluorescent stain of nasopharyngeal secretions was available. If this proved negative they were moved into the rest of the ward. Children on the ward developing respiratory symptoms were not transferred to this area unless they proved to be positive for the virus by indirect immunofluorescence. Where possible nurses who developed a respiratory illness were cohorted to care for babies in the respiratory syncytial virus area, but no formal attempt was made to diagnose the virus in staff. It was not possible to cohort babies on the paediatric intensive care unit. It has been hospital policy for nursing but not medical staff to wear gowns when handling infants under 1 year old, and change these between each infant, and this policy was not changed. Alcohol based hand rubs (Amphisept 80, Goldschmidt Ltd) were placed on each sink. Staff were instructed on the importance of handwashing and this was reinforced on ward rounds. A leaflet was prepared for parents (figure) detailing the way respiratory syncytial virus infection is spread, asking them to wash their hands and to keep older siblings with colds away from the play areas. A leaflet was given to the parents of every child admitted with the infection.

Statistical analysis was by Student's *t* test to compare means and by χ^2 or Fisher's exact test to compare incidence and severity of infection.

- **Your baby is in hospital with a condition called bronchiolitis.**
- This is caused by a virus called respiratory syncytial virus (RSV).
- The virus is usually caught from a brother, or sister or parent who has a cold or chestiness.
- The disease is very infectious and is passed on by infected nasal secretions carried on hands or toys but not usually by coughing. The secretions are rubbed into the nose or eyes to cause infections.
- The best way of preventing spread of RSV infection is, therefore, by washing your hands after handling your baby. If you have a cold yourself try to wash your hands before handling other children.
- Many children on the ward have conditions such as heart disease which can be made much worse by RSV infection. To prevent these children being infected please wash your hands. If you have an older child with a cold do not let them play in the play areas on the ward until they are better.
Thank you

Information leaflet given to parents.

Results

In 1986–7 (9 December to 26 March), before any intervention, there were 122 isolates of respiratory syncytial virus from study children. Altogether 101 isolates were from community acquired infections, 18 children had hospital acquired infections, and three with hospital acquired infection had recurrences. In 1987–8 (12 September to 11 April) there were 55 admissions with community and five with hospital acquired infection. In 1988–9 (18 October to 16 February) there were 115 admissions with community and six with hospital acquired infection (table 1).

During the first study period (1986–7) there were 425 children admitted to or present on the paediatric wards, excluding children admitted with respiratory syncytial virus infection, the latter not being considered at risk of acquiring the virus. The children stayed in hospital for a

Table 1 Occurrence of community acquired infections and hospital acquired infections of respiratory syncytial virus

Year	*Total admissions during epidemic*	*No (%) with community acquired infection*	*Remainder (at risk of hospital acquired infection)*	*No (%) with hospital acquired infection*
1986–7	526	101 (19)	425	18 (4·2)*
1987–8	895	55 (6)	840	5 (0·6)*
1988–9	667	115 (17)	552	6 (1·1)*

*1986–7 *v* 1987–8, χ^2=19·0, p<0·001; 1986–7 *v* 1988–9, χ^2=8·7, p<0·01; 1987–8 *v* 1988–9, χ^2=0·5, p=0·5.

Table 2 Duration of hospital stay for children with community acquired infection due to respiratory syncytial virus

Year	*Total days in hospital*	*Mean (SD) stay in days**	*Median stay in days*
1986–7	414	5·24 (4·27)	4
1987–8	259	4·71 (4·29)	3
1988–9	487	4·24 (4·25)	3

*No significant difference between years.

Table 4 Severity of community acquired infections with respiratory syncytial virus

Year	*Grade of severity*					*Total*
	1	*2*	*3*	*4*	*5*	
1986–7	49	20	8	21	3	101
1987–8	30	10	8	2	5	55
1988–9	62	26	20	6	1	115

$\chi^2=16{\cdot}4$, 6df, $p<0{\cdot}02$.

total of 1731 days within the study period, a mean (SD) stay of 4·05 (3·16) days with a median of 2 days. In the second study period (1987–8), which was a much longer outbreak, there were 840 such admissions for 3749 days, a mean (SD) stay of 4·46 (3·92) days and a median of 2 days. In the third study period (1988–9) there were 552 admissions for 2082 days, mean (SD) was 3·77 (3·69) days and median 2 days. Thus in the first study period 18 of 425 (4·2%) children exposed developed respiratory syncytial virus infection compared with five of 840 (0·6%) in the second period and six of 552 (1·1%) in the third period ($\chi^2=24{\cdot}3$, 2df, $p<0{\cdot}001$). The difference between the first and second periods ($\chi^2=19{\cdot}0$, 1df, $p<0{\cdot}001$) and between the first and third periods ($\chi^2=8{\cdot}7$, 1df, $p<0{\cdot}01$) was significant, but not between the second and third periods ($\chi^2=0{\cdot}5$, 1df, $p=0{\cdot}5$).

Children infected in the community with respiratory syncytial virus were hospitalised for a similar mean duration in each study period (table 2). The total duration of hospitalisation of children with community acquired infection was similar in 1986–7 and 1988–9, but was considerably less in 1987–8.

There was an increasing number of children under 2 years old admitted with congenital heart disease over the three year study period, concomitant with the appointment of a second cardiologist. In 1986–7 none of 12 children <2 years with congenital heart disease (excluding babies with community acquired infection due to respiratory syncytial virus) admitted for less than 14 days, but eight of 11 (72·7%) admitted for more than 14 days were infected with the virus in hospital (table 3). In 1987–8 one of 30 (3·3%) children with congenital heart disease became infected in hospital compared with eight of 23 (34·8%) in 1986–7 ($p<0{\cdot}008$, Fisher's exact test). In 1988–9 one of 47 (2·1%) became infected in hospital ($p<0{\cdot}0008$ compared with 1986–7).

Three children with congenital heart disease were admitted with community acquired infection due to respiratory syncytial virus in 1986–7, none in 1987–8, and seven in 1988–9. Three of the children with respiratory syncytial virus infection in 1986–7 had pulmonary hypertension, none in 1987–8, and four in 1988–9. There were no deaths attributable to infection with the virus. The mean (SD) duration of hospital stay of children under 2 years with congenital heart disease (excluding babies with community acquired infection) was not significantly different in the three study years: 33·6 (33·1) days in 1986–7, 33·7 (16·1) days in 1987–8, and 31·0 (18·2) days in 1988–9. The median stay was 21, 28, and 23 days respectively. Thus children with congenital heart disease were equally likely to be exposed to respiratory syncytial virus infection, other factors being equal, in each of the three years.

Table 3 Number of children <2 years old with congenital heart disease admitted to paediatric wards during respiratory syncytial virus season (number who developed a hospital acquired infection with the virus)

Year	*Duration of hospital stay (days)*			
	1–7	*8–14*	*>14*	*Total*
1986–7	7 (0)	5 (0)	11 (8)	23 (8)*
1987–8	19 (0)	5 (0)	6 (1)	30 (1)*
1988–9	26 (0)	9 (1)	12 (0)	47 (1)*

Children with congenital heart disease admitted with respiratory syncytial virus infection have been excluded.
*$\chi^2=24{\cdot}3$, 2df, $p<0{\cdot}001$.

The median duration of hospital stay of children with congenital heart disease before they developed respiratory syncytial virus infection was 14 days (range 8–114).

In 1986–7, four babies with chronic lung disease due to bronchopulmonary dysplasia developed respiratory syncytial virus infection (three infections acquired in hospital) and of two children with cystic fibrosis who developed the virus one infection was hospital acquired. In 1987–8 one baby with bronchopulmonary dysplasia became infected with the virus in hospital. In 1988–9 two babies with bronchopulmonary dysplasia were infected (one hospital acquired) and one child with cystic fibrosis had a community acquired infection.

The severity of infection acquired in the community in each of the study years is shown in table 4. A χ^2 analysis (combining grades 4 and 5 because of small numbers in these cells) showed that the severity of infection was not the same in each of the three years. There was no significant difference in severity between 1986–7 and 1987–8 ($\chi^2=4{\cdot}0$, 3df, $p>0{\cdot}2$), but infection with the virus was significantly more severe in 1986–7 than 1988–9 ($\chi^2=15{\cdot}8$, 3df, $p<0{\cdot}01$). In 1988–9 three babies with congenital heart disease and respiratory syncytial virus infection were treated with nebulised ribavirin, but ribavirin was not used for children in previous years nor for any other children in 1988–9.

Discussion

Nosocomial infections with respiratory syncytial virus are a major problem within hospitals,[5] particularly as children with serious underlying disorders who are at risk of severe infection may become infected. In one study the mortality for infants with congenital heart disease and respiratory syncytial virus was 37%, and 73% if they had pulmonary hypertension,[2] although subsequent studies including the current one would suggest the mortality has fallen substantially. The risk of nosocomial infection with the virus has previously been shown to rise with increasing duration of hospital stay.[2]

Prevention of hospital acquired respiratory syncytial virus infection depends on understanding how the infection is spread. Babies shed large quantities of virus for prolonged periods.[10] Adults can readily be reinfected, by rubbing infected secretions into their nose or eyes,[11] and act as a reservoir for the infection, which is probably important in infecting babies. Babies are most likely to be infected by contaminated nasal secretions, which have come from another infected baby or infected member of staff and are carried on the hands of staff.[12] Other possible mechanisms of spread include fomites, as respiratory syncytial virus can remain viable on environmental surfaces for several hours.[13] Respiratory droplet spread, however, is probably an unusual route of transmission.[12] This evidence suggests that efficient handwashing might be an effective way of preventing infections both in staff and babies. It has been recommended that gowns be worn when soiling of clothes with respiratory secretions is likely,[14] but we found an unacceptably high level of nosocomial respiratory syncytial virus infection despite following this suggestion. We do not have sufficient isolation rooms to isolate all infected babies, as has also been suggested.[14] Various interventions have been evaluated. Leclair and colleagues found that glove and gown isolation precautions were highly effective in preventing nosocomial respiratory syncytial virus infections,[6] but others have found gowns and masks to be ineffective.[8] Eye-nose goggles prevent staff infections over a short period but are unacceptable to staff.[7] There are obvious advantages to using handwashing and cohorting as the main methods for preventing infections. Many studies have shown that handwashing practises, even in intensive care units, are suboptimal and we have previously observed handwashing to be extremely poorly performed on paediatric wards. We did not formally examine compliance with handwashing, but feel the reduction in nosocomial respiratory syncytial virus infection is strong evidence that compliance was good.

In order to show convincingly that our interventions were effective in reducing nosocomial infection with the virus we need to show that there was comparable exposure in the three study winters. In 1987–8 the epidemic was much smaller and more drawn out than in the other two years, and children on the wards were less exposed to the virus. Thus the fall in the incidence of hospital acquired infection in 1987–8 alone cannot be attributed to our interventions. In 1988–9 there were more children admitted with community acquired infection than in 1986–7 over a similar period of time, however, and the total number of infections in the two winters was virtually the same. We did not evaluate duration of viral shedding in children with respiratory syncytial virus infection, but they were hospitalised for a comparable length of time each year. Leclair and colleagues estimated that children would shed virus for seven days, and calculated exposure on this basis.[6] On the other hand children often shed virus for much longer,[9] and neither they nor we formally examined this. As children with hospital acquired infection often remain in hospital because of their underlying illness they will expose other children, leading to a cascade effect if infections are not prevented. Another consideration is that the severity of the annual epidemics may vary from year to year, possibly as a result of different subgroups of respiratory syncytial virus being prevalent,[15] and more severe infections might be more contagious. We did not look at subgroups of the virus but we did examine severity by a clinical grading and found that respiratory syncytial virus infection was less severe in 1988–9 than in the two previous years. Despite this the number of admissions with community acquired infection due to the virus in 1988–9, and reports to the Communicable Disease Surveillance Centre for the three years, would suggest the respiratory syncytial virus epidemic was at least as large in 1988–9 as the two previous years and the virus no less contagious. We did not formally examine nursing levels, which might have influenced spread of infection. However these certainly did not improve between 1986–7 and 1988–9.

Our observations are not based on an ideal study design, as the data on the incidence of nosocomial respiratory syncytial virus infections before intervention were not collected prospectively. Our rate of nosocomial infection with the virus was unacceptably high, however, and we felt ethically constrained to intervene and then attempt to evaluate our intervention. Cases of respiratory syncytial virus infection were identified by positive viral cultures and the techniques used for identification did not change over the study period. Children were classified as having hospital or community acquired infection on strict criteria not amenable to bias. Nasopharyngeal aspirates are routinely taken from all children <2 years admitted with respiratory illness and from those hospitalised children who develop respiratory symptoms. Bias might have been introduced by failure to identify children with hospital acquired infection due to the virus after intervention, but we feel that increased awareness of respiratory syncytial virus infection generated by the study is more likely to have resulted in more rather than fewer cases of hospital acquired infection being identified.

We showed a reduction of at least 66% in the number of hospital acquired infections due to respiratory syncytial virus in the two winters after emphasising the importance of handwashing and simple cohorting of babies. Furthermore, despite comparable lengths of stay each year, we showed that the proportion of babies with congenital heart disease hospitalised for more than 14 days who acquired the infection fell from 73% to less than 4%. We acknowledge that we cannot prove that the decrease in incidence of infection with the virus was due to our interventions, but feel we have provided convincing circumstantial evidence to this effect.

One minor problem with cohorting was that babies could not remain in the accident and emergency department until a diagnosis of respiratory syncytial virus infection was virologically confirmed. Hence they were cohorted on the basis of a clinical diagnosis of bronchiolitis. In 1988–9 one baby with congenital heart disease and clinical bronchiolitis was cohorted in the respiratory syncytial virus area and subsequently shown to be negative for the virus. Despite being moved within 24 hours to the main ward and discharged home shortly thereafter the baby was readmitted within five days with respiratory syncytial virus positive bronchiolitis. This problem might be overcome if a more rapid antigen detection test for respiratory syncytial virus infection was available, and one hour tests are currently being evaluated.

Handwashing is simple, cheap, and highly effective in preventing nosocomial respiratory syncytial virus infections. We should make every effort to reinforce this message to staff and parents on the general paediatric wards as well as in the neonatal unit.

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Infant care at the Appeal Court

A very premature baby needed ventilator treatment for a month and two further periods of ventilation when he collapsed off the ventilator. At 4 months postnatal age he was breathing independently but was cyanosed when crying and prone to periods of apnoea. Ultrasound scans had shown 'very severe brain damage'. The child was a ward of court and a judge had agreed with the doctors' view that ventilation should be withheld if the child collapsed again. The Official Solicitor appealed on the child's behalf and the case went to the Court of Appeal on 19 October. (*The Daily Telegraph,* Law reports, 25 October 1990).

The Master of the Rolls, Lord Donaldson, with Lords Justice Balcombe and Taylor, upheld the judge's decision. Lord Donaldson said that, while there was a very strong presumption in favour of a course of action that would prolong life, the quality of life and the pain and suffering that the child would experience if life was prolonged also had to be taken into account. In the end there would be cases where the answer would be that it was not in the child's interests to subject it to treatment which would cause increased suffering and produce no commensurate benefit.

ARCHIVIST

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Association between urinary symptoms at 7 years old and previous urinary tract infection

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Abstract

The association between current micturition habits and previous urinary tract infection was analysed among 3553 school entrants aged 7 years by means of a questionnaire. A high incidence of urinary infection, confirmed by urine culture, was found (145 (8·4%) in the 1719 girls and 32 (1·7%) in the 1834 boys). There was a significant association between current symptoms that were suggestive of disturbed bladder function and previous urinary tract infection, but only among girls who were over 3 years of age at the time the first episode was diagnosed.

Urinary tract infections are common in children but the reason is often unknown. One factor of importance is inadequate emptying of the urinary bladder.[1] Residual urine was a common finding among schoolgirls with asymptomatic bacteriuria, and recurrences after treatment occurred significantly more often in those who had more than 5 ml of residual urine measured by an isotope technique.[2] Residual urine was also common among girls with acute cystitis.[3]

Another important abnormality in children with recurrent urinary infections is poor coordination between the detrusor and the sphincter.[4] Before the amount of residual urine is measured or urodynamic investigations are started, however, the symptoms of the child should be analysed. The most obvious symptom of bladder dysfunction is incontinence, which is associated with urinary infection.[5] [6] The incidence of other symptoms suggestive of bladder dysfunction is, however, not known. We therefore studied the association between current symptoms suggestive of bladder dysfunction and a history of previous urinary infections in an unselected group of 7 year old school entrants.

Subjects and methods

All Swedish children attend a health examination together with a parent and the teacher on entering school at the age of 7. Different problems are discussed with the school physician and the school nurse. Before this examination a health questionnaire is given to the families, to use as a basis for discussion. In 1982 an additional questionnaire about current micturition habits and urinary incontinence was given to all Swedish speaking school entrants in Göteborg by the school nurses.[7] Previous urinary infections and other diseases of the urinary tract were also investigated. If there was anything abnormal or unanswered in the questionnaire the family was contacted by telephone for more details by one of the investigators. Children with problems were offered further examination at the children's hospital.

Nocturnal as well as diurnal incontinence was defined as wetting at least once during a three month period. Urgency was defined as a short latent period between the first sensation and the need to void that occurred daily. Children who were able to postpone micturition voluntarily while they were occupied were not considered to have urgency. A specific question was asked about the use of a squatting position to prevent incontinence (the 'curtsy' sign[8]) and whether this was used at least once a week. A child was considered to have emptying difficulties when symptoms such as starting difficulties, poor or interrupted stream, straining or manual compression of the bladder, or prolonged micturition occurred more than twice a week.

The original records from hospitals and outpatient clinics of children who gave a history of urinary infections or other diseases of the urinary tract were studied, and the diagnosis of urinary tract infection re-evaluated. The growth of at least 10^5 bacteria/ml in voided urine, or any number in specimens of urine obtained by suprapubic aspiration, were required before the diagnosis of bacteriuria was made. A further classification of the infection was done according to clinical signs and laboratory findings. In children with fever of at least 38·5°C a diagnosis of acute pyelonephritis was made if the C reactive protein concentration was >20 mg/l, or if the concentrating capacity was transiently decreased.[9] The term 'cystitis' was used in children over 1 year of age with acute dysuria, temperature below 38·5°C, and normal laboratory findings. Some children could not be classified according to these criteria—for example, when laboratory tests were normal or not carried out in children with fever and bacteriuria. These infections were diagnosed as 'unspecified urinary infections'. For 'asymptomatic bacteriuria' at least two urine cultures in which the same bacteria were grown, but in the absence of symptoms, were required.

Fisher's exact test was used for statistical analysis.

Results

In 1982 a total of 3627 Swedish speaking children born in 1975 entered school in Göteborg, and 3607 questionnaires were distributed. Of these 3556 (98·6%) were completed and returned, 48 refused to complete them, and three families had moved abroad. Three children with malformations were excluded (myelomeningocele, epispadia, and anal atresia with fistula to the urinary tract) leaving 3553 questionnaires for analysis (1719 girls and 1834 boys).

PREVIOUS URINARY TRACT INFECTIONS

Previous urinary tract infection was reported in 274 children, but from the original records, bacteriuria was confirmed in only 177: 145 girls and 32 boys (table 1). The median ages at the time of first infection were 4 years for girls and 0·8 years for boys. The infections were classified as acute pyelonephritis (n=66), cystitis (n=65), and asymptomatic bacteriuria (n=11). In addition, there were 35 children whose infections could not be classified retrospectively (unspecified urinary infection). In the latter group, 21 children had had fever of 38·5°C or more but laboratory tests such as C reactive protein concentration and renal concentrating capacity were either normal or not carried out.

In 28 girls and 11 boys a diagnosis of urethritis had been made because of acute symptoms of micturition without appreciable bacterial growth. The remaining 58 children had been examined because of various symptoms and urine cultures had grown no pathogens.

BLADDER SYMPTOMS ASSOCIATED WITH PREVIOUS URINARY INFECTIONS

At least one symptom was reported by 919 of the 7 year old school entrants (26%), the distribution being similar in both sexes. Isolated bed wetting occurred in 48 of the girls (2·8%) and 129 of the boys (7·0%). Isolated bed wetting did not correlate with a history of previous urinary infection. In contrast, girls with daytime wetting, urgency, squatting, and emptying difficulties had had previous urinary infections significantly more often than those without (table 2). Among the boys there was no such difference.

Among the girls with symptoms, previous urinary infections had occurred most often in those with squatting (15 of 41) and emptying difficulties (eight of 22), 36% in each group (fig 1). In girls with diurnal incontinence previous infection was reported by 31 (30%) and in those with urgency by 46 (13%). In contrast, only one of 48 girls (2%) with isolated bed wetting had had a urinary infection. Seventeen of 74 girls with bed wetting combined with daytime symptoms (23%), however, had had urinary infections.

Table 1 Number (%) of children who had had previous urinary tract infections according to sex and diagnosis

Diagnosis	*Girls (n=1719)*	*Boys (n=1834)*	*p Value*
Pyelonephritis	47 (2·7)	19 (1·0)	<0·001
Cystitis	59 (3·4)	6 (0·3)	<0·001
Unspecified urinary tract infection	29 (1·7)	6 (0·3)	<0·001
Asymptomatic bacteriuria	10 (0·6)	1 (0·1)	<0·01
Total	145 (8·4)	32 (1·7)	<0·001

Table 2 Current symptoms in girls who did and did not have previous urinary tract infections

	No (%) who had previous urinary tract infections (n=145)	*No (%) who had not had previous urinary tract infections (n=1574)*	*p Value*
Isolated bed wetting	1 (0·7)	47 (3·0)	>0·05
Daytime wetting	31 (21·4)	72 (4·6)	<0·001
Urgency	46 (31·7)	314 (19·9)	<0·01
Squatting	15 (10·3)	26 (1·7)	<0·001
Emptying difficulties	8 (5·5)	14 (0·9)	<0·001

The frequency of micturition did not differ between children with and without previous infections (mean 4·5 micturitions/day in each group).

AGE AT TIME OF FIRST URINARY INFECTION AND BLADDER SYMPTOMS

Of the girls who had infections during the first year of life, five (19%) at age 7 had symptoms suggestive of bladder dysfunction compared with 18 (49%) of those with first urinary infection at age 3 to 5 years (p<0·05) (fig 2).

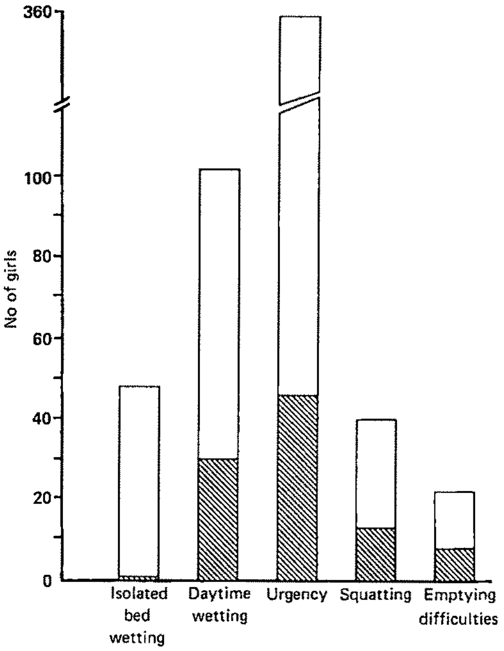

Figure 1 Proportion of girls reporting current symptoms with a history of previous urinary infection (hatched area).

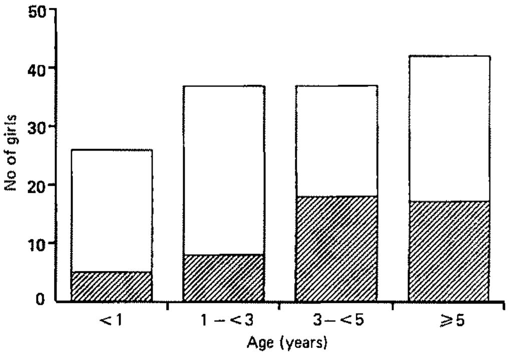

Figure 2 Number of girls with previous urinary infections according to age at the time of first known infection. The hatched areas indicate girls reporting symptoms suggestive of bladder dysfunction at 7 years of age.

RECURRENCE OF INFECTION AND BLADDER SYMPTOMS

Fifty seven girls (39%) and four boys (13%) had had recurrent infections, and these were not related to age at the time of diagnosis of the first urinary tract infection. Symptoms suggestive of bladder disturbance (incontinence, urgency, squatting, and emptying difficulties) at 7 years of age were reported in 23 (40%) of the girls with recurrences compared with 27 (26%) in those with single episodes of infection; this difference is not significant.

Discussion

In this study of 7 year old Swedish children, a history of previous urinary tract infection was verified in 145 of the 1719 girls (8·4%) and 32 of the 1834 boys (1·7%). These figures are higher than previously reported among similar children. In an epidemiological study of children with symptomatic urinary infection in Göteborg in 1960–6, Winberg *et al* recorded an overall morbidity of 2·8% in girls and 0·7% in boys up to 11 years of age.[10] Our higher figures are, however, corroborated by another recent study from Göteborg in which acute pyelonephritis was found in 3·1% of the girls and 1·0% of the boys up to the age of 6 years.[11] This high detection rate probably reflects the increased awareness among the population and the physicians, and the common habit of culturing urine routinely in feverish infants and young children.

This study shows a clear association between the presence of bladder symptoms and a history of bacteriologically verified urinary infections in girls. Those who had had previous urinary infections reported significantly more symptoms suggestive of dysfunction of the lower urinary tract than those who had not. As many as one third of the girls who complained of daytime wetting, squatting, or emptying difficulties had had at least one episode of urinary infection in the past.

In contrast, girls with isolated bed wetting were at low risk of urinary infection; they also had normal frequency of micturition. This suggests that children with isolated bed wetting constitute a separate group from those who have symptoms during the day. The distinction is important, because the need for investigation of the urinary tract is highest among those with daytime symptoms, especially when combined with a history of urinary infections.

The age at which the first infection was diagnosed was of importance in the incidence of bladder symptoms. Girls who were over 3 years old at the time of their first infection had significantly more symptoms suggestive of bladder dysfunction at the age of 7; such an association was not found among girls whose urinary infections started when they were younger. Among boys there was no statistical association between symptoms and previous urinary infection. One probable explanation is the young age at which the boys had their first infection (median 0·8 years compared with 4.0 years in girls).

What is the basis for the association between urinary tract infection and bladder dysfunction? Which comes first? The design of this investigation did not allow us to evaluate the relative importance of these factors. It may be that an infection of the urinary tract during the period when bladder control is becoming established is a potential threat to the normal development of this control. Pain caused by urogenital inflammation may lead to a suppression of micturition resulting in disturbed function of the lower urinary tract and subsequently to an increased susceptibility to bacterial colonisation. On the other hand, dysfunction may be the first event. We often see patients who seem to have a primary 'hold' pattern affecting both the bowel and the bladder. This can lead to inefficient emptying of the bladder with residual urine and an inability to eliminate ascending bacteria.

Whatever the causal relationship may be, regular and complete emptying of the bladder and regular bowel habits are important in the prevention of urinary tract infections.

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Social environment and height: England and Scotland 1987 and 1988

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Abstract

This study was designed to investigate the social characteristics associated with the height of primary schoolchildren aged from 5 to 11. Data were analysed for 8491 representative sample children measured in England and Scotland in 1987 and 1988 and 3203 inner city children measured in England in 1987. Height was negatively associated with social class but the association was not significant after allowing for biological variables. A negative gradient of height with size of sibship was evident in white children but was less so in Afro-Caribbean and Asian children. The individual associations of 11 different environmental characteristics were examined after allowing for biological factors and size of sibship. Consistent associations with height included a negative gradient of height with increasing latitude and an association of taller stature with increasing maternal age. A social class gradient in height is accounted for by associations with biological factors, particularly the parental heights; environmental attributes are weakly associated with height after allowing for biological factors.

Children's height is a sensitive indicator of their physical wellbeing, and has been recommended as a measure of their nutritional state.[1] Associations between height and environmental characteristics have been investigated as possible indications of adverse influences on growth. In such investigations a number of variables including the paternal social class[2–7] and employment,[5] the family size,[4 5] the number of parents at home,[8] and the presence of overcrowding[8] have been used to characterise social conditions during childhood.[2] A gradient associating height with social class has been documented both in adults[3] and children,[4–7] but the existence of a gradient does not itself indicate a direct influence on growth. An association between height and a given social characteristic is difficult to interpret because of the number of confounding variables among the social characteristics of the child's environment and between social and biological factors. It is necessary to adjust for confounding variables with multiple regression analysis but this raises the question: what confounding variables should be allowed for in such analyses?

The National Study of Health and Growth is a surveillance study which was set up in 1971 to monitor the growth of primary schoolchildren in England and Scotland.[9] In 1983 a second (inner city) sample was recruited.[8] Reports from this study have shown associations between height and a number of characteristics of the social environment including paternal social class and employment,[5 8] type of school meals,[10] presence of overcrowding in the home, and the educational attainment of the mother.[8] The selection of variables for inclusion in these analyses has, however, been inconsistent.

We therefore undertook the present analyses to examine the problem of confounding variables in more detail. We aimed to define the variables that should be included in analyses and to re-examine the association between children's height and paternal social class for children living in England and Scotland in 1987 and 1988.

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Subjects and methods

SUBJECTS

Two samples were recruited into the National Study of Health and Growth. The initial sample included children from schools in 22 employment exchange areas in England and 14 in Scotland, which were selected by stratified random sampling.[9] The characteristics of children from this sample are similar to those of the general population,[8 11] and the sample will be referred to as 'representative' in this paper.

The inner city (selective) sample was selected by identifying 10 electoral wards in England with high incidences of overcrowding, male unemployment, or shared household amenities. In addition five wards were selected each of which had a high proportion of families from Asian backgrounds, and five each of which had a high proportion of families from Afro-Caribbean backgrounds. The wards that were selected because of their ethnic composition are also inner city areas with characteristics of deprivation. For the present analysis, data measured in 1987 were analysed for the inner city sample and data measured in 1988 for the English representative sample together with that measured in 1987 and 1988 for the Scottish children. Data for the small number of non-white children in the representative sample were exluded from analysis as were data from children aged less than 5 or over 11 years on their last birthday.

METHODS

The methods used in the survey have been described previously.[9] Children were measured at school by school nurses, 10% of measurements were checked by a full time fieldworker from the study team. Height was measured using a portable Holtain stadiometer to the last complete 0·1 cm.[12] The ethnic group of the child was classified according to the language spoken at home and by the fieldworker's subjective assessment of the child's ethnic group.[8] The child's parent or guardian was asked to complete a self administered questionnaire containing questions relating to the child's health and the social background of the family. The questionnaire also requested information concerning the adult heights of the child's parents and the child's birth weight.

ANALYSIS

Parental heights and the child's birth weight are of greatest importance in explaining the variations in childrens' height; cases containing missing values on these continuous variables were therefore excluded from analysis. For categorical variables a 'not known' category was defined for each variable. Height standard deviation (SD) scores were used for the analysis of children's heights. The score was calculated for each child as the difference between the child's height and the mean height for English representative sample children of the same age and sex divided by the SD for that group. This method of expression standardises for age and sex and for the increasing variation in height with age. One SD score is roughly 5–7 cm between the ages of 5 and 11 years.

Categorical variables were classified as follows. The length of pregnancy was grouped into four categories: less than 38 weeks, 38 to 42 weeks, more than 42 weeks, or 'not known'. The number of children in the family was grouped into six categories: one, two, three, four children, five or more, or 'not known'. The age of the mother at the child's birth was categorised as: less than 20, 20 to 23, 24 to 27, 28 to 31, over 32, or 'not known'. The birth order of the child (the number of older siblings) was used as a proxy for maternal parity. In the inner city sample the ethnic group of the child was classified into seven categories: white, Afro-Caribbean, Urdu, Gujarati, Punjabi, other Asian, 'other' and 'not known'.

Paternal social class was defined by the Registrar General's classification, which for analysis was reduced to the following categories: non-manual, skilled manual, semiskilled and unskilled manual; a category for families headed by a single mother; not applicable and not known. Maternal social class was defined by the mother's present or previous occupation and was classified into: non-manual, skilled manual, semiskilled and unskilled manual, full time housewife, other, or not known. Paternal employment was divided into: employed, unemployed less than 12 months, unemployed more than 12 months, unemployed (duration unknown), not applicable and not known. Maternal employment was divided into: employed, not employed, at home, not applicable and not known. The hours worked by the mother outside the home were categorised as: less than 15/week, 15 to 25, more than 25, no outside work, or not known. Maternal educational attainment was divided into: primary, secondary, commercial or technical, university, no school education, or not known. Mother's age at finishing full time education was divided into the following categories: less than 12 years, 12 to 16 years, 17 to 19 years, 20 to 23 years, 24 or more, not applicable or not known.

The receipt of benefits included unemployment benefit, income support, and family credits; it was classified as received, not received, or not known. The receipt of free school meals was classified into received, not received, not applicable and not known. The degree of overcrowding in the home was estimated by dividing the number of people in the accommodation by the number of rooms (excluding kitchen and bathroom). This index was categorised into five groups: less than 1 person per room, 1 to 1·24, 1·25 to 1·49, 1·50 or more, or not known. A categorical variable was also included for country of residence (England or Scotland).

The independent associations between explanatory variables and height SD scores were estimated by multiple linear regression analysis. To take into account the potential for mutual confounding of the variables, the analysis was undertaken in three stages. Firstly, the unadjusted association between paternal social class and the children's height was examined. Secondly, a model was constructed to include all the biological variables that were independently associated with height. This model included the parental heights, the child's birthweight, the reported length of pregnancy, the birth order and the child's ethnic group (for the inner city sample). The country of residence was also included in this model for the represen-

Table 1 Height SD score by paternal social class in the representative sample and the ethnic groups of the inner city sample. Values are expressed as unadjusted mean (SE) height SD score

Ethnic group	*No of subjects*	*Paternal social class*			*Single mother*	*Not known*
		I-IIIA Non-manual	*IIIB Skilled manual*	*IV-V Semiskilled and unskilled manual*		
Representative sample:						
England	5117	0·105 (0·023)	0·000 (0·024)	−0·024 (0·039)	0·016 (0·043)	−0·067 (0·050)
Scotland	3374	0·062 (0·030)	−0·048 (0·029)	−0·074 (0·042)	−0·103 (0·052)	−0·072 (0·075)
Inner city sample:						
White	1397	0·043 (0·078)	−0·236 (0·051)	−0·303 (0·059)	−0·167 (0·057)	−0·351 (0·070)
Afro-Caribbean	388	0·603 (0·166)	0·499 (0·118)	0·187 (0·171)	0·527 (0·082)	0·712 (0·112)
Urdu	112	−0·055 (0·244)	−0·359 (0·167)	−0·123 (0·208)	−0·685 (0·398)	−0·534 (0·167)
Gujarati	271	−0·510 (0·174)	−0·516 (0·104)	−0·749 (0·131)	0·454 (0·469)	−0·718 (0·131)
Punjabi	616	−0·027 (0·114)	−0·137 (0·075)	−0·067 (0·069)	−0·001 (0·189)	−0·271 (0·089)
Other Asian	120	−0·553 (0·258)	−0·086 (0·193)	−0·387 (0·213)	−0·457 (0·301)	−0·412 (0·225)
Other	299	−0·140 (0·155)	0·191 (0·141)	−0·138 (0·169)	0·553 (0·178)	−0·385 (0·130)

tative sample. The sibship size was also included in this model because of its strong association with children's height. The resulting model was used to adjust individually the associations of each of the remaining social characteristics with height SD score.

Finally all these social variables were included simultaneously and their independent effects assessed using a stepwise procedure with backward elimination of the least associated variable at each step. A conservative probability of 0·10 was used to retain variables in this model.[13] In each analysis the height SD scores of the children were used as the dependent variable. Independent variables were entered as continuous variables except where the categorisation of the variable had previously been indicated.

Results

Data for the representative sample and for the inner city sample were analysed separately. Data from 11 267 representative sample children (mean height SD score −0·015) measured in England in 1988 or in Scotland in 1987 and 1988 were available for analysis. After excluding cases containing missing values on continuous variables 8491 cases (mean height SD score 0·009) were analysed. For the inner city sample measured in England in 1987, 6580 cases (mean height SD score −0·168) were available for analysis; after excluding cases containing missing values 3203 cases (mean height SD score −0·133) were analysed.

Among English representative sample children there was a significant gradient in height with paternal social class (F=4·42; df 4,5112, p=0·001) (table 1). Children living in Scotland were shorter than English children (F=6·13, df 1,8489, p=0·013). The association of height and paternal social class was also significant for Scottish children (F=3·21, df 4,3369, p=0·012). For the inner city sample there was also a gradient of height by paternal social class, although this was not independent of ethnic group (table 1). White inner city children were shorter than white representative sample children allowing for differences in social class (F=35·61, df 1,9869, p<0·001).

Adjusting for biological variables (parental heights, length of pregnancy, birth weight, and ethnic group) eliminated the association between social class and height in England and Scotland. Additional analyses showed that adjusting for parental heights alone was sufficient to account for the social class gradient in height. Adjusting for parental heights alone also accounted for the difference in height between the representative sample and inner city white children in each social class category, but differences in height between the ethnic groups remained significant after adjusting for parental heights (F=31·74, df 6,11680, p<0·001).

Both the birth order and size of sibship were associated with children's heights. Height increased with increasing birth order (after adjusting for size of sibship) but the effect of size of sibship was quantitatively more important. In both England and Scotland there was a negative association between size of sibship and height SD score (table 2). In the inner city sample a trend towards decreasing height with increasing size of sibship was also seen for white children, but in the Asian and Afro-Caribbean children this gradient was diminished or absent. The first order interaction between ethnic group and size of sibship was significant (F=8·09, df 41,3161, p<0·001).

The individual associations of height SD scores with social attributes, adjusted for parental heights, birth weight, length of pregnancy, size of sibship, birth order, and country of residence (representative sample) or ethnic group

Table 2 Height by size of sibship. Values are expressed as unadjusted mean (SE) SD score

Size of sibship	*English representative*	*Scottish representative*	*English inner city*	*Afro-Caribbean*	*Asian*
1	0·260 (0·051)	0·117 (0·061)	0·180 (0·091)	0·526 (0·138)	−0·123 (0·213)
2	0·067 (0·020)	0·051 (0·025)	−0·121 (0·048)	0·619 (0·114)	−0·036 (0·078)
3	−0·014 (0·028)	−0·087 (0·033)	−0·311 (0·057)	0·468 (0·119)	−0·309 (0·063)
4	−0·082 (0·046)	−0·244 (0·055)	−0·316 (0·074)	0·511 (0·139)	−0·231 (0·074)
≥5	−0·007 (0·061)	−0·171 (0·086)	−0·522 (0·096)	0·438 (0·154)	−0·374 (0·058)

Table 3 Individual associations between height SD score and social variables each adjusted for parental heights, birth weight, length of pregnancy, size of sibship, birth order, and country of residence (representative sample) or ethnic group (inner city sample)

Independent variable	*Representative sample*			*Inner city sample*		
	F	*df*	*p Value*	*F*	*df*	*p Value*
Paternal social class	1·13	4	0·339	0·66	4	0·617
Paternal employment	1·32	4	0·260	4·62	5	<0·001
Maternal age	4·15	5	<0·001	4·92	5	<0·001
Maternal social class	0·56	4	0·690	4·56	4	0·002
Maternal employment	3·32	3	0·019	6·17	3	<0·001
Maternal hours of work	1·50	4	0·199	4·81	4	<0·001
Maternal education	1·13	5	0·342	2·06	5	0·068
Overcrowding	1·76	4	0·134	0·92	4	0·454
Benefits	1·22	2	0·295	6·89	2	0·001
School meals	1·38	3	0·247	9·40	3	<0·001
Longitude	0·31	1	0·579	26·78	1	<0·001
Latitude	16·16	1	<0·001	27·70	1	<0·001

(inner city sample) are shown in table 3. For the representative sample shorter stature was associated with younger maternal age at the child's birth and with the mother not being currently employed. The latitude of residence was also associated with height.

The use of the stepwise procedure resulted in the selection of the parental heights, the child's birth weight, length of pregnancy, size of sibship, latitude and country of residence, maternal age, and employment position as significant associations of height (table 4). For the inner city sample, after adjusting for biological factors, ethnic group and size of sibship, taller stature was associated with: father currently employed, mother currently employed, older age of the mother, non-manual occupation of the mother, and the mother working more than 25 hours/week outside the home. Shorter stature was associated with the receipt of benefits including free school meals and with increasing latitude or longitude of the study area (table 3). The use of the stepwise procedure resulted in the selection of the parental heights, the child's birth weight, the length of pregnancy, the birth order, size of sibship, ethnic group (interacting with size of sibship), maternal age, type of school meals, and latitude and longitude of residence as significant associations with height (table 5).

Table 4 Model defined using stepwise procedure for representative sample. Values given are coefficient (SE) for continuous variables and mean difference (SE) from last mentioned category for categorical variables, each adjusted for every other variable

Independent variable	*Coefficient (SE)*	*F ratio*
Intercept	−17·697 (0·535)	
Maternal height (cm)	0·048 (0·001)	1072·9
Paternal height (cm)	0·041 (0·001)	991·9
Birth weight (kg)	0·332 (0·019)	308·5
Latitude (°N)	0·031 (0·007)	19·2
Length of pregnancy:		
<38 weeks	0·194 (0·041)	10·8
38–42 weeks	0·041 (0·031)	
>42 weeks	−0·310 (0·196)	
Not known	0	
Country of residence:		
England	0·069 (0·034)	4·2
Scotland	0	
Size of sibship:		
1	0·144 (0·055)	13·0
2	0·003 (0·047)	
3	−0·075 (0·048)	
4	−0·147 (0·054)	
⩾5	−0·194 (0·064)	
Not known	0	
Maternal age:		
⩽19	−0·133 (0·124)	4·9
20–23	−0·144 (0·119)	
24–27	−0·126 (0·118)	
28–31	−0·078 (0·118)	
⩾32	−0·013 (0·119)	
Not known	0	
Maternal employment:		
Employed	0·011 (0·055)	3·5
Not employed	−0·183 (0·089)	
At home	−0·032 (0·056)	
Not known	0	

Residual mean square 0·71, df 8469.

Table 5 Model defined using the stepwise procedure for the inner city sample. Values given are coefficient (SE) for continuous variables and mean difference (SE) from last mentioned category for categorical variables, each adjusted for every other variable

Independent variable	*Coefficient (SE)*	*F ratio*
Intercept	−10·117 (1·006)	
Maternal height (cm)	0·039 (0·002)	256·9
Paternal height (cm)	0·031 (0·002)	216·4
Birth weight (kg)	0·360 (0·032)	124·7
Latitude (°N)	−0·044 (0·016)	7·6
Longitude (°W)	−0·049 (0·020)	5·7
Length of pregnancy:		
<38 weeks	0·127 (0·059)	4·6
38–42 weeks	−0·062 (0·042)	
>42 weeks	−0·152 (0·328)	
Not known	0	
Ethnic group, size of sibship, and interaction	42 levels not shown	4·3
Birth order:		
1	−0·026 (0·078)	2·1
2	−0·152 (0·078)	
3	−0·100 (0·084)	
4	−0·129 (0·097)	
5+	−0·194 (0·102)	
Not known	0	
Maternal age:		
⩽19	−0·031 (0·119)	2·4
20–23	−0·006 (0·109)	
24–27	0·029 (0·109)	
28–31	0·104 (0·112)	
⩾32	0·175 (0·113)	
Not known	0	
School meals:		
Not free	0·210 (0·066)	4·3
Free	0·077 (0·061)	
Other	0·139 (0·068)	
Not known	0	

Residual mean square 0·84, df 3140.

Discussion

These data show that the heights of primary schoolchildren vary according to country of residence, ethnic group, and paternal social class. The analysis was designed to identify environmental characteristics that were independently associated with height.

In the representative sample a large proportion of the explained variation in children's heights is accounted for in association with parental heights.[4 5] For the inner city sample the associations of birth weight and parental heights accounted for a smaller proportion of the variation in children's heights.[8] This may be partly accounted for by the greater variation in the child's social and ethnic background but it has also be shown that the validity of the parents' self reported heights is less among the inner city sample.[14] After allowing for parental heights, birth weight, length of pregnancy, and country or ethnic group, the gradient in height with social class was not significant; these biological factors account for much of the social class variation in children's height.

The association between the heights of parents and children is well documented and is compatible with a genetic mechanism.[15] The influence of a common family environment cannot be discounted,[16] but the finding of a strong parent-child association in height that accounts for the social class gradient tends to argue against an immediate environmental cause of social class differences in height during childhood. There is evidence that selection of social class by height does occur,[17] but social mobility also seems to have a quantitatively small effect in determining social class gradients in height.[18]

There does not seem to be a strong intergenerational association for birth weight,[19] but environmental factors may have important influences on growth in the antenatal period and account for some of the variation in height at older ages.[20] Although there is an association between increasing birth order and increasing height,[21] our findings show that this is less important than the negative association with size of sibship. Birth order was not selected as having an independent association with height for the representative sample, and was only weakly associated with height when selected by the stepwise procedure for the inner city sample. The pattern of association between the number of children in the family and height varied between the different ethnic groups. In each of the samples of white children (English representative, English inner city, and Scottish) height diminished with increasing family size. Among Afro-Caribbean children and Asian children the gradient of height with size of sibship was reduced or absent.

The mechanism for the effect of family size on height is not well established. It has been suggested that economic factors are responsible,[2] smaller amounts of poorer quality food being available to children from larger families.[22] In the National Study of Health and Growth a higher proportion of children in the ethnic minority groups come from larger families.[8] The finding that the gradient of height with size of sibship is less in these groups suggests that the patterns of child care are also differently associated with family size in the ethnic groups. Simons (in a study of Sikhs living in London) found that although actual family size was not significantly greater than that of the white population, Sikhs preferred larger families including male children.[23] Thus one characteristic of larger families from the ethnic minorities that might distinguish them from white families is that they are planned.

After allowing for biological factors, ethnic group, and family size the association of other social characteristics of the children were of small magnitude. More were significant in the inner city sample than in the representative sample. The age of the mother at the time of the child's birth was significantly associated with height in each of the samples and was consistently selected by the stepwise procedure. There was a gradient of increasing height with increasing age of the mother at the time of the child's birth. This association was reported previously by the National Study of Health and Growth[5] and has been described in other surveys.[4 24] The recent trend towards increasing maternal age[25] may be one of the factors associated with the secular trend towards increasing height in Britain.[26] It is also relevant that there is a trend towards decreasing postneonatal mortality with increasing maternal age, and this observation is also compatible with an effect of maternal age on child care.[27]

Paternal unemployment is known to be associated with children's height,[5] but in these analyses we found that this association was not significant in the representative sample after adjusting for parental heights, birth weight, length of pregnancy, size of sibship, birth order, and country of residence. The effect of maternal employment on children's development has been the subject of debate.[28 29] Here, the employment position of the mother was associated with taller stature of primary school children. The receipt of free school meals was strongly associated with shorter stature for children in each sample but after adjustment this was significant only in the inner city sample.

In each of the samples, children's height diminished with increasing latitude of the study area, which is consistent with the gradient observed in the adult population.[30] In the inner city sample height kept a negative association with latitude after adjusting for confounding variables, but for the representative sample the direction of the gradient was reversed after this adjustment. The gradient in height with latitude in this sample is thus more than accounted for by the other confounding variables.

Size of sibship is the social characteristic showing the strongest association with height, although the nature of this association depends on the ethnic background. Other social characteristics were of only marginal importance. Among the variables examined, the age of the mother at the time of the child's birth and the latitude of residence were consistently associated with height across the two samples. The receipt of free school meals and nonemployment of the mother were also associated with shorter stature. These analyses help to characterise the variables that should be included in adjustment for confounding, when attempting to characterise influences on growth during childhood; they also emphasise the greater importance of biological compared with social factors as influences on height for children living in England and Scotland.

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St Vitus, Sydenham, and the Bruegels

For over 400 years (13th to 17th centuries) a strange form of hysterical crowd behaviour occurred in Europe. This was the dancing mania, the original St Vitus' dance. Crowds of people would suddenly begin to dance in circles and continue to the point of exhaustion. Their stomachs would swell and some would fall to the ground as if in an epileptic seizure (R H R and M P Park, *Journal of the Royal Society of Medicine* 1990;**83**:512–5).

Two saints were named as protectors of these people, St John the Baptist and St Vitus, but later St John became associated with epilepsy and St Vitus with the dancing mania. Sufferers from the dancing affliction were prone to relapse on the saints' feast days (24th and 15th June).

Vitus is first mentioned in the 5th century. He was the son of a senator in Sicily and preached in southern Italy, was credited with expelling a demon from the son of the Roman Emperor Diocletian, was tortured, and eventually suffered martyrdom.

The *Epileptic Women of Molenbeek* is a pen and ink drawing in the Albertina in Vienna copied by the younger Bruegel from the work of his father. It depicts sufferers not from epilepsy but the dancing mania who are about to be cured by being thrown off a low bridge into the water near to St John's chapel. The cure apparently lasted a year.

Why Thomas Sydenham applied the name of St Vitus to acute chorea is not clear. He probably lived too late to have seen the severe form of dancing mania (chorea imaginativa of Paracelsus) but may have seen a minor form of the disorder which Paracelsus called chorea naturalis and borrowed the term 'St Vitus's dance' from that.

Treatment of Sydenham's chorea

While on the subject of St Vitus's dance, a report from Kuwait (Daoud *et al*, *Neurology* 1990;**40**:1140–1) suggests sodium valproate as a treatment for acute chorea. Thirteen of 15 children responded completely within a week. One 7 year old who responded had had chorea for two years and had previously failed to respond to haloperidol, chlorpromazine, phenobarbitone, and diazepam.

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Sucking on the 'emptied' breast: non-nutritive sucking with a difference

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Abstract

A simple method to promote the use of human milk and subsequent breast feeding in low birthweight infants was evaluated in 32 babies. In the 'intervention' group (n=16; mean (SD) weight 1559 (228) g and length of gestation 33·2 (1·8) weeks), infants were allowed to suckle at the breast when their general condition permitted after as much milk as possible had been expressed, and were then given the full required feeds by tube. Full breast feeding was started as soon as the infant could suck adequately. Sixteen control infants (mean (SD) weight 1605 (198) g and length of gestation 34·1 (2·4) weeks), were breast fed in the conventional manner only after it had been established that they could suck well; until then they received all their feeds by tube. After discharge the mean (SD) periods of exclusive and total breast feeding were longer in the group that had received the intervention (3·7 (1·3) and 5·1 (2·2) months, respectively) than among the controls (1·9 (0·6) and 3·3 (1·9) months, respectively).

This 'intervention' method helps to promote milk formation, provides sucking experience for low birthweight infants without interfering with their nutritional intake and consequent weight gain, and encourages subsequent breast feeding with its well recognised advantages.

When human milk is used to feed low birthweight infants, continued flow of milk may present problems especially if weight and gestation are low, the suck is weak, and the period of separation long. Maternal anxiety and medical problems make things worse. Giving the mothers emotional support by encouraging early contact and participation in the nonspecialised care of their infants is helpful.[1 2]

Initiating and maintaining breast feeding in a young low birthweight infant before he or she is fully ready for it may result in inadequate weight gain or even weight loss, and supplementing nutrition by tube feeding when the stomach is partially full after an attempted breast feed can create its own problems. We observed that low birthweight infants could suckle at the breast after as much milk as possible had been expressed, and could then be given the full required feeds by tube. This study was set up to evaluate this intervention, which we called suckling on the 'emptied' breast.

Patients and methods

Thirty two low birthweight infants weighing less than 1800 g who could not accept direct breast feeding were enrolled in the study. Infants who could be enterally fed after delivery were tube fed with intermittent boluses through an orogastric tube (the routine in the unit). Sick and very low birthweight infants initially received parenteral glucose electrolyte solutions, and enteral feeds were started as soon as their condition permitted; the volume was gradually increased to 200 ml/kg. Infants usually received their own mothers' milk supplemented where required by suitable donor milk. If human milk was inadequate, supplementary milk feeds using a locally available partially adapted formula were given. During this period another study was in progress in the unit to evaluate weight gain with human milk enriched by the addition of local powdered milk formula (unpublished observations), and hence some infants were receiving the latter.

The intervention itself comprised the following steps: the mother was asked to express the milk as completely as possible from both breasts (in the unit manual expression was practised as is common in developing countries)[3]; the infant was then put to the breast in a warm room and allowed to suckle. Finally the full calculated volume of milk was given by intermittent bolus by the orogastric route.

In the pretesting phase it was noted that excessive sucking in the early stages sometimes resulted in inadequate weight gain or even weight loss. Initially, therefore, sucking was permitted for only a brief period. The number of episodes and sucking time were gradually increased, care being taken to monitor the weight daily until the infants were allowed to suck for as long as they wanted to before tube feeds, the end point being when the infant stopped sucking on his own. As infants became stronger, full breast feeding was started and this gradually replaced the combination of 'emptied' breast sucking and tube feeding. A single bottle feed was tried to start with to judge the infant's sucking capacity before initiating full breast feeds.

Control infants were treated in a similar manner as far as intermittent tube feeds were concerned, and were also given to mothers to hold and cuddle. They were, however, put to the breast in the conventional manner only after it had been established that they could suck adequate volumes from trial feeds; gradually, then, all tube feeds were replaced by breast feeds. The bottle was not used routinely for giving breast milk.

An attempt was made to allot alternate mothers to the intervention and control groups, but this was impossible as the procedure so caught the fancy of mothers that whenever they saw another mother carrying out the procedure they insisted on following suit. We therefore evaluated a small group of mother–infant pairs (n=8) as controls treated in the conventional manner and after all these had been discharged we initiated the intervention group (n=8) and then repeated the cycle. Permission was obtained from mothers for the intervention, but it was merely a formality. Statistical analysis was by Student's *t* test and the χ^2 test as appropriate.

Results

The hospital where the study was carried out catered to a mixture of social classes. As statements regarding income were invariably unreliable, emphasis was laid on maternal education; this is shown in table 1 together with other maternal characteristics such as age, experience of breast feeding, presence of older women in the home, and outside employment. In the intervention group 81% and in the control group 88% had had some form of education. There were no signifient differences between the groups for any of the variables.

The intervention could be started when an infant was aged 10 (2) days. Initially tiny preterm babies merely 'mouthed' the nipple when put to the breast but they soon established definite sucking, which subsequently was noted to be well sustained with bursts of sucking activity alternating with periods of rest. No infant had any episodes of choking during the interventions or during the subsequent introduction of the feeding tube. Aspiration before starting feeds showed either no milk or—in older infants—less than 5 ml.

Table 2 shows characteristics of the infants. Again there were no significant differences between the two groups in sex distribution, mean birth weight, gestation, or presence of early neonatal problems such as birth asphyxia, respiratory distress, or hyperbilirubinaemia. The duration of parenteral fluids and the various types of milk feeds were similar in the two groups, as were the weight at discharge and duration of hospital stay.

A separate evaluation of the weight gain was made among infants weighing less than 1500 g (10 in the intervention group and nine among controls). As shown in the figure weight gain was similar in the two groups. Table 3 shows the final outcome noted at follow up, which was carried out until breast feeding was completed. Three babies in the intervention group and six controls were already receiving supplementary milk feeds at the time of discharge. Two infants in the control group were not breast fed at all after discharge, the mothers saying that they did not have sufficient milk. These differences, however, were not significant in this sample

Table 1 Maternal characteristics

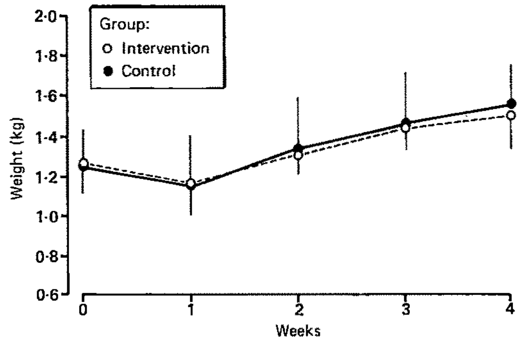
	Intervention group (n=16)	*Control group (n=16)*	t/χ^2	*p Value*
Mean (SD) age (years)	27·5 (3·6)	28·6 (3·6)	t=0·87	>0·05
Education:				
Nil	3	2	χ^2=0·05	>0·05
School	3	4		
College	10	10		
Breast feeding experience	9	20	χ^2=0·13	>0·05
Residential older women	7	9	χ^2=0·50	>0·05
Outside employment	5	2	χ^2=0·73	>0·05

Table 2 Infant characteristics

	Intervention group (n=16)	*Control group (n=16)*	t/χ^2	*p Value*
No of boys	9	11	χ^2=0·53	>0·05
Mean (SD) birth weight (g)	1559 (228)	1605 (198)	t=0·62	>0·05
Mean (SD) gestation (weeks)	33·2 (1·8)	34·1 (2·4)	χ^2=1·21	>0·05
No with early neonatal problems	5	4	χ^2=0	>0·05
No on parenteral fluids	10	9	χ^2=0·13	>0·05
Mean (SD) duration (days) of parenteral feeding	11·5 (3·5)	11·8 (4·1)	t=0·22	>0·05
Milk feeds:				
Expressed human milk alone	5	5	χ^2=0	>0·05
Enriched expressed human milk (see text)	5	6	χ^2=0·14	>0·05
Expressed human milk and formula	6	5	χ^2=0·14	>0·05
Mean (SD) discharge weight (g)	1752 (100)	1742 (135)	t=0·24	>0·05
Mean (SD) hospital stay (days)	24·3 (9·5)	23·1 (9·8)	t=0·36	>0·05

Table 3 Outcome

	Intervention group (n=16)	*Control group (n=16)*	t/χ^2	*p Value*
No on artificial milk at discharge	3	6	χ^2=0·62	>0·05
No not breast fed after discharge	—	2		
Mean (SD) duration of exclusive breast feeding (months)	3·7 (1·3) (n=13)	1·9 (0·6) (n=10)	t=4·05	<0·001
Mean (SD) duration of total lactation (months)	5·1 (2·2) (n=16)	3·3 (1·9) (n=14)	t=2·35	<0·05



Patterns of weight gain in infants weighing less than 1500 g in the intervention group (n=10) and the control group (n=9). The values are expressed as mean (SD).

size. On the other hand, the period of exclusive breast feeding and the total duration of lactation were significantly longer in the intervention group.

Discussion

In 1983 Bernbaum *et al* noted that sucking on a pacifier enhanced the maturation of the sucking reflex, improved weight gain, and even reduced hospital stay.[4] Paediatricians in developing countries usually discharge low birthweight infants far earlier than their Western counterparts. A higher proportion of mature infants with retarded growth in the Third World is one of the reasons that we are able to initiate oral feeds earlier.[5] Overcrowding and potential risk of infection in some units are additional motivating factors for early discharge. Under these circumstances the use of pacifiers to stimulate the more premature and very low birthweight infants cannot be recommended because their use is likely to be perpetuated and could further predispose to infection, particularly after discharge from the hospital, as well as interfere with breast feeding.

The potential risk of HIV infection has unfortunately had a detrimental influence on the use of donor breast milk, and policies not only vary in different units, but need to be revised periodically to suit changing local requirements. Wherever breast milk is used, however, promotion of subsequent breast feeding must also be a priority.

A number of methods have been tried to initiate early oral feeding both in hospitals and in the community in the Third World. The innovative 'kangaroo' method with close early contact and start of breast feeding has aroused considerable interest.[6] The use of a spoon, cup,[7] or an easily cleaned traditional feeding device[8] are also widely used in developing countries. A controlled trial of skin to skin contact by the kangaroo method in a developed country has also shown that it has a beneficial influence on breast feeding.[9] Preterm infants are handicapped by their limited intakes, initially poor ability to suck, and speed with which they tire, and a balance has to be maintained between energy intake and expenditure so that optimal weight gain can be ensured. Excessive physical stress, as in early initiation of breast feeding, may result in inadequate intake and poor weight gain. This applies even to sucking on the 'emptied' breast described in this paper, as excessive sucking in the early stages may not be suitably compensated for by the nutritional intake.

Interestingly, Bernbaum *et al* attributed the increased weight gain that they noted in infants who sucked pacifiers to one or more of the following reasons: sucking was believed to stimulate secretion of sublingual lipase with associated improved fat absorption from formulas; it also resulted in better oxygenation and decreased restless activity.[4] These findings were supported by Field *et al*[10] and Measel and Anderson.[11] In the present study, however, we did not note an improved weight gain in the infants. Possible explanations for this finding could be that raw human milk containing lipases was the main milk used in both groups and also that even control infants had some sucking experience as they tended to suck on the orogastric feeding tube. The recent study by Ernst *et al* has also failed to show improved weight gain and decreased hospital stay with non-nutritive sucking on a pacifier.[12] When the sucking is at the breast, however, the impact on lactation that we have shown in this study seems to be appreciable. In developed countries where mothers and staff are motivated to use human milk, continuation of milk flow and emotional satisfaction should be benefits. In developing countries, use of human milk has a significant influence on the infective morbidity and mortality in high risk infants.[13] Even in units where infections may not be a major problem it is still important to ensure that the long term outcome is acceptable if the resources and efforts expended on these infants at risk in the neonatal special care unit are to be justified. In this context longer periods of exclusive and total lactation can influence more long term infective morbidity after discharge particularly among the less privileged groups,[14] and emotional satisfaction is an added bonus.

As noted earlier, most of the mothers in this study had had some education. In the Third World it is this group that does not seem to be so successful in sustaining lactation,[15] and hence the findings in this report are all the more important.

We have since found this intervention to be of use also in larger full term infants who are convalescing from illnesses such as birth asphyxia, respiratory distress, or major infections, at a stage when the infants are improving but are not strong enough to accept full direct breast feeds. The weaker, younger, smaller, and more preterm infants do not suck strongly enough to swallow any appreciable volumes, and the few ml sucked by the stronger, older, larger, and more mature ones not only contain the fat rich hind milk,[16] but also do not seem to interfere with subsequent tube feeds. With better observation even 'trial' bottle feeds can be dispensed with, as the occurrence of good sustained sucking at the emptied breast can be made out to determine the stage at which direct breast feeding can be introduced.

In conclusion, this is a simple intervention, which is useful not only to stimulating sucking but also to promote maternal milk flow and prolonging lactation in mothers of high risk infants, with all its attendant benefits.

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Prorenin and diabetes

Outside the entrance to our hospital there appeared a large poster proclaiming that Susan stands in the shadow of diabetes and its complications. The need to collect money, it seems, overrides any possible adverse effect on young patients of such advertising even in the minds of those who run the national charity for people with diabetes.

A prime aim of treating childhood diabetes must be to prevent the adult complications if possible and several ways of identifying diabetic children at risk have been proposed.[1] Fifteen years ago Dr John Luetscher and colleagues at Stamford University, California, reported finding 'big renin' in the plasma of diabetic patients with nephropathy,[2] and in a recent article in the *New England Journal of Medicine* (1990;**323**:1101–6) Wilson and Luetscher show that plasma prorenin activity is raised in children who later develop retinopathy or nephropathy. They studied 135 patients in a children's diabetic clinic. Albuminuria or retinopathy began to appear from the age of 12 years. About 80% of the patients who developed these complications had raised plasma prorenin at some time and this could be found in some patients up to three years before the appearance of the complication though in others the latent interval was apparently much shorter.

There seems to be little point in measuring plasma prorenin before the age of 10. Young children have relatively high values, which gradually decline to between 9 and 12 years of age. In this study young children who initially had values above the normal limit for age had normal values on repeat testing.

Over the age of 10 a high plasma prorenin may precede microangiopathy. It remains to be seen whether attempts at better diabetic control in these patients might prevent or delay the complications.

ARCHIVIST

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Physical activity patterns defined by continuous heart rate monitoring

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Abstract

To investigate the physical activity patterns of British primary schoolchildren (mean (SD) 10·7 (0·3) years) the minute by minute heart rates of 67 boys and 65 girls were monitored continuously for three 12 hour periods during normal schooldays. In addition 39 children had their heart rates monitored during a 12 hour period on a Saturday. Few children experienced the volume (frequency, intensity, and duration) of physical activity associated with an improvement in cardiopulmonary fitness. Shorter (five minute) periods of the required intensity were, however, quite common. No difference between moderate amounts of activity was detected between boys and girls, but the boys had more five minute sessions of intense activity than the girls. These findings suggest that more research into the effects of short periods of intense physical activity on the cardiopulmonary systems of young children is required and that the determinants of habitual physical activity require further investigation especially in the context of sex differences at such an early age.

A recent review of the published physical activity recommendations for children concluded that appropriate physical activity for children should entail large muscle groups moving dynamically for periods of 20 minutes or longer, three or more times/week, at an intensity that elicits heart rates equal to or in excess of 140 beats/minute.[1] This recommendation correlates with the amount of physical activity suggested by Morris *et al* as being associated with a low incidence of coronary heart disease in adults.[2] Other reviewers, however, have indicated that more intense exercise—up to 80% of maximum heart rate (roughly 160 beats/minute)—is necessary for the improvement of children's cardiopulmonary fitness.[3] Whether British primary schoolchildren regularly undergo these amounts of physical activity is unknown.

Interpretation of published reports about children's physical activity patterns is beset with problems caused by the inherent difficulty of defining the quality and quantity of children's physical activity. Reliable data are limited and must be interpreted according to the methods used. The 'self report' (by retrospective questionnaire or daily diary) of the intensity and duration of periods of activity by children is difficult because children are less conscious of time than adults and tend to engage in physical activity that is sporadic, both in time and intensity. Ideally the relative intensity and duration of activities should be immediately and simultaneously assessed. The monitoring technique must be socially acceptable, it should not burden the child with cumbersome equipment, and it should have a minimal influence on the child's normal physical activity patterns. Bar-Or suggested that if a true picture of habitual physical activity is required, at least three days of monitoring are necessary.[4] No investigation of habitual physical activity among British primary schoolchildren that satisfies these criteria to our knowledge has been carried out. This study was therefore designed to examine the physical activity patterns of such children, aged 10 years.

Subjects and methods

SUBJECTS

Written informed consent to participate in the project was obtained from the parents and all the children in the sixth year at five primary schools in Devon. The children's age was computed from date of birth and date of physical activity assessment. Height was measured with an anthropometer (Cranlea Medical) calibrated against a Harpenden stadiometer (Holtain), and weight was determined on scales (Griffin and George) calibrated against a beam balance (Avery 3306 ABV).

ASSESSMENT OF PHYSICAL ACTIVITY

The volume (frequency, intensity, and duration) of physical activity of 67 boys and 65 girls was estimated from continuous heart rate monitoring over three normal schooldays. Physical activity is not directly measured in this way, but—perhaps more importantly—the relative stress being placed upon the cardiopulmonary system by the activity is monitored. For ease of exposition, however, it will be assumed that volume of heart rate response is indicative of volume of physical activity.

A self contained, computerised telemetry system (Sport Tester 3000) was used to record continuously heart rates minute by minute. The Sport Tester 3000 consists of a lightweight transmitter, which is fixed to the chest either by a belt or with electrodes, and a receiver/microcomputer, which is worn as a watch on the wrist. It is a reliable and valid way of recording heart rates in children,[5] and a recent survey of the most popular commercially available heart rate monitors concluded that the Sport Tester 3000 was first choice as 'in addition to having excellent validity and stability it permits almost total freedom of motion’.[6] The Sport Tester 3000 is capable of storing and replaying minute by minute heart rates for up to 16 hours and if it is interfaced with a microcomputer a simple programme permits sustained periods when heart rates are above selected thresholds to be readily identified and recorded. Each child was monitored from about 0900 until 2100 during a normal schoolday. The receivers were retrieved, replaced, and refitted the next morning and the process was repeated for three days. In addition 39 of the children (16 boys and 23 girls) were monitored from 0900 until 2100 on a Saturday.

Results

The data were stored and analysed using RS1 database (BBN Software Products Corporation) installed on an IBM-PC. Descriptive statistics were computed and the significance of differences assessed by the appropriate *t* test.

The physical characteristics of the children are shown in table 1. There were no significant differences ($p>0\cdot05$) between the girls and boys in age, height or weight, or between girls and boys in the percentage of time they spent with heart rates above 139 beats/minute during either weekdays (boys 9·4%, girls 8·2%) or Saturdays (boys 5·2%, girls 6·0%). The boys, however, spent a significantly higher percentage of time ($p<0\cdot05$) with heart rates above 159 beats/minute during weekdays (boys 4·5%, girls 3·5%) but not during Saturdays (boys 1·8%, girls 1·8%).

Table 1 Physical characteristics of the children. Values are expressed as mean (SD)

	Boys (n=67)	*Girls (n=65)*
Age (years)	10·7 (0·3)	10·7 (0·3)
Height (m)	1·4 (0·06)	1·4 (0·07)
Weight (kg)	35·3 (5·7)	36·2 (7·1)

Table 2 Number (%) of children and number of periods when they achieved heart rate of >139 beats/minute during three days of weekday monitoring

	Boys (n=67)	*Girls (n=65)*
5 Minute periods:		
0	1 (1)	0
1	2 (3)	6 (9)
2	4 (6)	4 (6)
≥3	60 (90)	55 (85)
10 Minute periods:		
0	13 (19)	16 (25)
1	10 (15)	18 (28)
2	13 (19)	11 (17)
≥3	31 (46)	20 (31)
20 Minute periods:		
0	41 (61)	43 (66)
1	12 (18)	14 (22)
2	7 (10)	7 (11)
≥3	7 (10)	1 (2)

Table 3 Number (%) of children and number of periods when they achieved heart rate >159 beats/minute during three days of weekday monitoring

	Boys (n=67)	*Girls (n=65)*
5 Minute periods:		
0	5 (7)	10 (15)
1	6 (9)	17 (26)
2	12 (18)	9 (14)
≥3	44 (66)	29 (45)
10 Minute periods:		
0	31 (46)	36 (55)
1	13 (19)	16 (25)
2	7 (10)	5 (8)
≥3	16 (24)	8 (12)
20 Minute periods:		
0	52 (78)	51 (78)
1	10 (15)	11 (17)
2	3 (4)	3 (5)
≥3	2 (3)	0

Table 4 Number (%) of children and number of periods when they achieved heart rate >139 beats/minute during one day of weekday monitoring

	Boys (n=16)	*Girls (n=23)*
5 Minute periods:		
0	7 (44)	10 (43)
1	5 (31)	5 (22)
2	2 (13)	1 (4)
≥3	2 (13)	7 (30)
10 Minute periods:		
0	12 (75)	15 (65)
1	4 (25)	4 (17)
2	0	0
≥3	0	4 (17)
20 Minute periods:		
0	13 (81)	22 (96)
1	3 (19)	1 (4)
2	0	0
≥3	0	0

Table 5 Number (%) of children and number of periods when they achieved heart rate >159 beats/minute during one day of weekday monitoring

	Boys (n=16)	*Girls (n=23)*
5 Minute periods:		
0	11 (69)	17 (74)
1	3 (19)	3 (13)
2	2 (13)	1 (4)
≥3	0	2 (9)
10 Minute periods:		
0	13 (81)	21 (91)
1	3 (19)	2 (9)
2	0	0
≥3	0	0
20 Minute periods:		
0	14 (88)	23 (100)
1	2 (13)	0
2	0	0
≥3	0	0

The interpretation of continuous heart rates is complex because not only is the metabolism of the child reflected, but also the transient emotional state, the prevailing climatic conditions, and the specific muscle groups that perform the activity. Therefore although the percentage of time spent in various heart rate ranges is of interest, we think that the primary consideration should be the number and length of sustained periods above selected thresholds. Accordingly we have analysed the number (%) of children who have sustained five minute, 10 minute, and 20 minute periods with heart rates above 139 beats/minute and 159 beats/minute during weekday and weekend monitoring (tables 2, 3, 4, and 5). The boys had significantly more 5 minute periods with their heart rate above 159 beats/minute during weekday monitoring ($p<0\cdot05$) but there were no other significant differences between the sustained heart rate response of boys and girls ($p>0\cdot05$).

Discussion

Few children spent daily periods of 20 minutes or longer with their heart rates above the recommended thresholds, indicating that sustained periods of physical activity for this length of time are not features of children's habitual physical activity. A similar analysis of 10 minute periods also showed that only a minority of children spent a daily session with their heart rates above the recommended levels. When 5 minute periods were examined, however, it was shown that most of the children had daily sessions of this length when their heart rates exceeded 139 beats/minute and two thirds of the boys and almost half of the girls had a daily 5 minute period when their heart rates exceeded 159 beats/minute. Over half of the children had a five minute period on a Saturday with their heart rates over 139 beats/minute, although only a small minority elicited heart rates of over 159 beats/minute for this length of time. It is therefore obvious that the physical activity patterns of primary schoolchildren consist of relatively short periods of physical activity, perhaps as a result of their limited attention span.

To put these figures into perspective it is noteworthy that with children of this age we have found that brisk walking on the treadmill at 6 km/hour elicits steady state heart rates in excess of 140 beats/minute and jogging at 8 km/hour generates steady state heart rates of over 160 beats/minute. Our results therefore indicate that although there seems to be no difference in moderate activity (equivalent to brisk walking) of boys and girls, boys experience more short intense periods of physical activity than girls.

No previously published study that we know of has reported the unobtrusive heart rate monitoring of British primary schoolchildren for extended periods of time. Direct comparisons of our data with those from elsewhere are difficult because of the different methods used, and because of our emphasis on the importance of sustained periods of physical activity. In a study from the Netherlands Saris developed a heart rate integrator and used the instrument in a biannual, 24 hour, analysis of 217 boys and 189 girls over a six year period beginning when the children were 6 years old.[7] He concluded that, at all ages, boys had a higher total energy expenditure and spent more time above 50% of maximal aerobic power than girls. Atomi *et al* monitored the 12 hour heart rates of 11 Japanese boys aged 10·4 years during three 'rainless days in winter' with a heart rate memory recorder.[8] They reported that boys spent on average 4·7% of their time at heart rates equivalent to 60% of maximal aerobic power.

The most quoted studies of the physical activity of primary schoolchildren are, however, those carried out by Gilliam *et al* with 6 and 7 year old children in the United States.[9–11] In their initial study they monitored the heart rates of 22 boys and 18 girls from 0800 until 2000 during a summer day. Both boys and girls had heart rates of more than 160 beats/minute for 2·9% and 1·3% of the time, respectively. The boys had heart rates of more than 140 beats/minute for 7·8% of the time and the girls for 4·0% of the time. In an intervention study in which they used the same methods and probably studied some of the same children, they reported that on average 59 children aged 7 years old spent 6·9% of their time with heart rates above 140 beats/minute.[10 11] They concluded that young children seldom undergo physical activity of high enough intensity to promote cardiovascular health, and that boys are more active than girls.

The physical activity patterns reported here compare favourably with those of children from elsewhere. Our data confirm the finding that boys experience more sessions of intense activity than girls, but we have detected no difference in moderate activity between the two sexes. Primary schoolchildren rarely experience periods of physical activity of the duration recommended for the improvement of cardiopulmonary fitness. More research into the effects of relatively short periods of intense physical activity on the cardiopulmonary systems of young children is required. The determinants of children's habitual physical activity must be further investigated, especially in the context of sex differences at such an early age.

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Urinary 3-hydroxyproline excretion in Alport's syndrome: a non-invasive screening test?

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Abstract

Alport's syndrome is characterised by morphological and structural changes of the renal basement membranes. As the hydroxyproline content of isolated glomerular basement membranes is reduced in patients with Alport's syndrome, it is possible that the renal excretion of 3-hydroxyproline (3-OHP), a key substrate of basement membrane collagen, may be altered in such patients. The urinary excretion of 3-OHP was determined by thin layer chromatography in 20 patients with Alport's syndrome, in healthy control subjects, and in patients with other renal diseases. These included patients with post-streptococcal glomerulonephritis, lower urinary tract infection, severe reflux nephropathy, lithium induced nephropathy, polycystic kidney disease, familiar benign haematuria, and renal graft rejection. Urinary excretion of 3-OHP was significantly higher in patients with Alport's syndrome compared with the patients with other renal diseases and the healthy control subjects. All other renal diseases investigated had 3-OHP values within the normal range. Urinary 3-OHP determination detected patients with Alport's syndrome with a high sensitivity (95·2%) and specificity (97·2%). We therefore suggest using urinary 3-OHP determinations as a simple non-invasive screening test for Alport's syndrome.

Alport's syndrome, a hereditary disorder, is characterised by morphological and structural changes of the renal basement membranes. Morphologically, electron lucent and electron dense areas, cloudy networks, fraying, splitting, thickening, distortion, and thinning of the lamina densa may be observed by electron microscopy.[1] However, the underlying mechanisms and molecular defects of the disease are still unclear.

Collagen type IV, an integral component of the glomerular basement membrane,[2] is immunologically different in patients with Alport's syndrome compared with healthy subjects.[3–5] Hydroxyproline, a major constituent of collagens, was reported to be reduced in isolated glomerular basement membranes of patients with Alport's syndrome.[6] Hydroxyproline exists in two stereoisomeric 'trans' forms: 4-trans-hydroxyproline (4-OHP) and 3-trans-hydroxyproline (3-OHP) but, unlike other connective tissue collagens, basement membranes normally contain large amounts of 3-OHP.[7] As 3-OHP is excreted with the urine, changes in the collagen metabolism of the renal basement membranes could be reflected by a different urinary excretion of 3-OHP.

In order to test this hypothesis, and to find out characteristic differences, we studied the urinary excretion of 3-OHP in patients with Alport's syndrome, in healthy control subjects, and in patients with other renal diseases.

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Patients and methods

Urine samples of 20 patients with Alport's syndrome were obtained from Sint Radboud-ziekenhuis, Institute foor Kindergeneeskunde, Nijmegen, The Netherlands. The median age of these patients was 16 years (range 4 days–57 years). There were 15 females and five males. The diagnosis was confirmed by the presence of albuminuria (20/20), by familial history (18/20), and/or by electron microscopy (10/20).

There were two groups of control subjects. The first group consisted of healthy control subjects and comprised 23 newborn infants (age 2–30 days), 11 infants (age 1–12 months), 16 toddlers (age 1–4 years), 47 children and adolescents (age 8–18 years), and 12 adults (age 22–41 years). The second group consisted of subjects with other renal diseases and comprised 10 children with acute and 10 children with chronic poststreptococcal glomerulonephritis, 10 children with haemorrhagic lower urinary tract infection, 10 children with severe reflux nephropathy (reflux grade 4), 10 adults with lithium nephropathy, five children with adult type polycystic kidney disease, seven children with familiar benign haematuria, and five children with acute renal graft rejection (10 urine samples). Urine samples consisted of spontaneously voided urine or of aliquots of a 24 hour collection period.

We determined the type of proteinuria (high/low molecular weight proteinuria) by polyacrylamide gel electrophoresis (PAGE) of the urine samples from the patients with Alport's syndrome. PAGE was performed according to standard principles using 8% polyacrylamide gel, molecular weight markers, and staining with coomassie blue.

The urinary concentration of 3-OHP was determined by thin layer chromatography. Urine samples were centrifuged at 3000 *g* for five minutes at room temperature and the supernatant used. The urinary volume used for chromatography was determined according to its creatinine content, which was analysed by Jaffé's method (Astra Beckman (R) Automatic Analyzer, Beckman). The volume containing 1 mg creatinine was added to 1 ml of 0·1 M phosphate buffer, pH 7·0, and 1 mg of charcoal

(Sigma C 5385). This mixture was vortexed for 20 seconds and centrifuged at 2000 *g* for 10 minutes at room temperature. The pellet was resuspended in 1 ml of 0·1 M phosphate buffer, pH 7·0, centrifuged again at 2000 *g* for 10 minutes. The pooled supernatants were applied to columns containing 3 ml of Dowex 50 W X 8 (Bio Rad 745-6441), 100–200 mesh, in hydrogen form. Amino acids were eluted with 2 ml of 4 M ammonia. The eluate was evaporated until dryness on a Pierce Reactitherm Heating Module and redissolved in 200 µl distilled water. An aliquot of 100 µl of this solution was added to 20 µl o-phthalaldehyde (30% triethylamine, 70% ethanol, 8 mg/ml, Pierce 26·010). The mixture was incubated at room temperature in the dark for 30 minutes and then evaporated until dryness. The samples were redissolved in 20 µl 0·1 M phosphate buffer pH 7·0. Adding 20 µl 7-chloro-4-nitrobenz-2-oxa-1,3 diazole (8 mg dissolved in 1 ml ethanol), the samples were heated in a waterbath for 10 minutes at 40°C. The samples were spun for 5 minutes at 2000 *g*. Ten µl of the resulting supernatant were applied to HP thin layer chromatography plates (LHP-KF Whatman 4806). The development solution consisted of acetone:chloroform:methanol: triethylamine=20:60:12·5:7·5). The plates were read at 365 nm on a Shimadzu TLC scanner CS 920; 4-trans-hydroxyproline (Sigma H 60·002), 4-cis-hydroxyproline (Sigma H 1·637), 3-trans-hydroxyproline, and 3-cis-hydroxyproline (synthesised by J Häusler[8]) were used as standards.

Specificity of the determinations on thin layer chromatography of 3-OHP was confirmed by high pressure liquid chromatography (HPLC) and by gas chromatography-mass spectrometry (GC-MS) in the standards used for the chromatography and in the urine samples obtained from the healthy adults. For the HPLC determinations checkpot samples, taken from the thin layer chromatography, were dissolved in elution buffer and characterised on reverse phase chromatography according to Lindblad and Diegelmann.[9] For the GC-MS determinations N-trifluoroacetly-O-trimethylsilyl-hydroxyproline-trimethylsily-esters were prepared according to Donike,[10] GC-MS determinations were performed on a Varian MAT 112 according to Vycudilik and Lubec.[11] The hydroxyprolines were characterised by two techniques: (i) monitoring of the M-15 fragment ion (m/e) 356, single ion monitoring (SIM) and (ii) analysis of the full mass spectra taken along with the GC separation of the derivatives at a rate of 1 sec/mass decade.

Differences between groups and within groups were analysed by the Kruskal-Wallis test.[12] Sensitivity of the 3-OHP determinations for detecting Alport's syndrome was defined as the proportion of patients with Alport's syndrome having a 3-OHP value above the range of the mean+2 SD of the 3-OHP values of the normal control subjects. Specificity of 3-OHP determinations for detecting Alport's syndrome was defined as the proportion of control subjects and of patients with other renal diseases having a 3-OHP value within the range of the mean and 2 SD of the normal control subjects.

Results

Polyacrylamide gel electrophoresis showed non-significant unspecific high molecular weight (= glomerular) proteinuria in 12/20 patients with Alport's syndrome.

Results of the thin layer chromatography determinations of 3-OHP are shown in the table and in fig 1 and 2. They were highly significant differences between the 3-OHP values of the patients with Alport's syndrome compared with the normal control subjects and with the patients with other renal diseases but no difference between the latter and the normal control subjects.

In a single patient with Alport's syndrome the 3-OHP excretion was within the normal range (mean, 2 SD) of the healthy control subjects, and five control subjects had a 3-OHP value above the 2 sigma range of the healthy control subjects. All patients with other renal diseases had 3-OHP values within the normal range. Thus a specificity of 97·2% and a sensitivity of 95·2% of the thin layer chromatography 3-OHP determinations may be calculated for the patients with Alport's syndrome.

Results of the 3-OHP determinations

Group	*No of subjects*	*Concentrations of 3-OHP*	
		Mean (SD)	*Range*
Alport's syndrome	21	5·64 (2·43)*†	1·97–10·24
Normal controls:	98	0·96 (0·59)	0·06–2·55
Adults	8	0·34 (0·14)	0·06–0·55
Children	40	1·08 (0·40)	0·52–2·40
Infants	11	1·50 (0·47)	0·91–2·55
Newborns	23	0·36 (0·13)	0·20–0·60
Toddlers	16	1·44 (0·64)	0·32–2·34
Other renal diseases:	82	1·05 (0·30)	0·41–2·10
Acute glomerulonephritis	10	0·94 (0·22)	0·47–1·21
Chronic glomerulonephritis	10	1·09 (0·38)	0·74–2·10
Urinary tract infection	20	0·96 (0·21)	0·47–1·43
Reflux nephropathy	10	1·23 (0·25)	0·72–1·57
Lithium nephropathy	10	0·98 (0·29)	0·41–1·33
Polycystic kidneys	5	0·94 (0·48)	0·53–1·72
Familiar benign haematuria	7	1·24 (0·30)	0·78–1·74
Graft rejection	10	1·07 (0·30)	0·54–1·48

*Significantly different from control group (p<0·0001).
†Significantly different from other renal diseases group (p<0·0001).

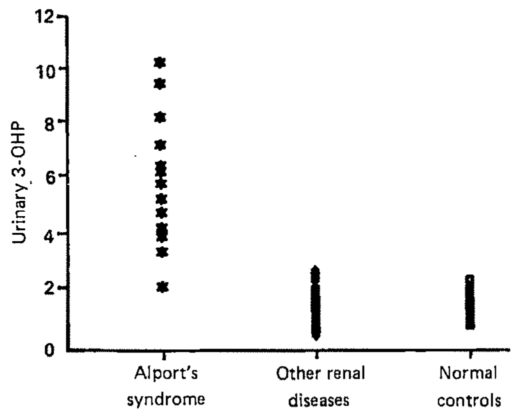

Figure 1 Determinations of 3-hydroxyproline (3-OHP) µg/mg creatinine by thin layer chromatography in patients with Alport's syndrome (n=20), patients with other renal diseases (n=67), and normal control subjects (n=109).

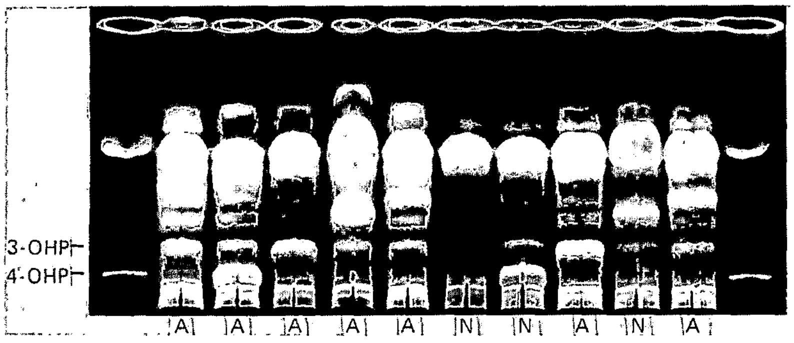

Figure 2 Thin layer chromatogram of 3-hydroxyproline (3-OHP) in patients with Alport's syndrome (A), in normal control subjects (N), and of hydroxyproline standards (4-OHP=4-trans-hydroxyproline).

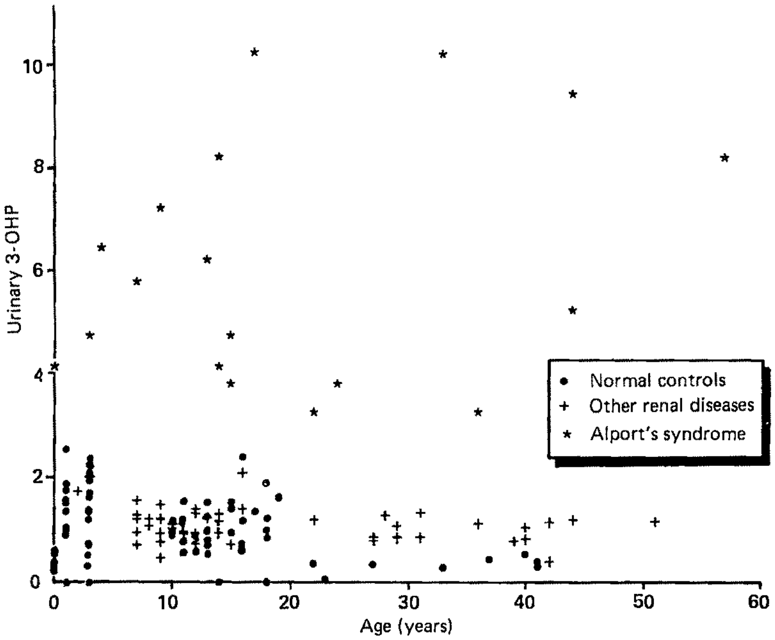

Figure 3 Relation between 3-hydroxyproline (3-OHP) µg/mg creatinine and age of the patients with Alport's syndrome (n=20), patients with other renal diseases (n=67), and normal control subjects (n=109).

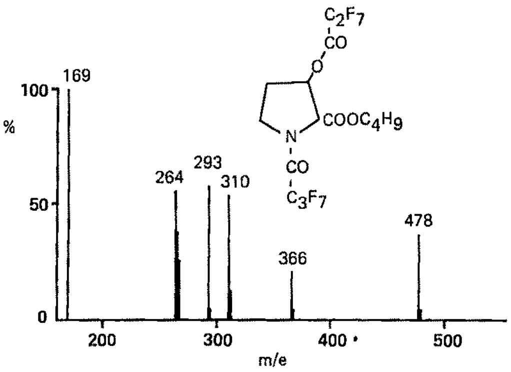

Figure 4 GC-MS spectrum of 3-hydroxyproline.

Among the normal control subjects there were significant differences between the 3-OHP values of the different age groups (Kruskal-Wallis test, $\chi^2=62{\cdot}98$, $p<0{\cdot}0001$), owing to a higher 3-OHP excretion in children, toddlers, and infants (see table). There were no significant differences of the 3-OHP values among the patients with various renal diseases. We found no correlation between age and 3-OHP values in the patients with Alport's syndrome, in the normal controls, nor in the patients with other renal diseases (fig 3).

The identification of the 3-OHP bands by thin layer chromatography was confirmed by HPLC and GC-MS determination in all 12 urine samples investigated (fig 4).

Discussion

This is the first report about an increased excretion of 3-OHP in patients with Alport's syndrome. There are reports on differences of the excretion of other amino acids: Tina *et al*[6] and Veltischev *et al*[13] found an increased urinary excretion of glycosylated hydroxylysine, another amino acid which may be found in collagens of basement membranes in relatively low amounts. However, this was not confirmed by Schröder *et al.*[14] Borel *et al* found an increased 3-OHP excretion in patients with other renal diseases—like glomerulonephritis—where proliferation and damage of the basement membranes are likely to occur.[15] In the latter study the total concentration of 3-OHP was determined in samples of hydrolysed urine, however, whereas we determined the urinary concentration of free 3-OHP. Hydrolysis may also involve remnant cells, micro-organisms, and cell and other debris. Moreover, treatment with acids may cause isomerisation of trans hydroxyproline to its cis form and thus lead to erroneous results.[16]

HPLC and GC-MS determinations showed that the described method of thin layer chromatography accurately measured 3-OHP. We related the urinary 3-OHP concentration to the urinary creatinine excretion in order to rule out differences in renal clearance and to avoid long lasting urine collection periods. Although the urine samples of the patients with Alport's syndrome were transported frozen, we cannot rule out that freezing may have caused degradation processes. According to our experience, however, repeated freezing and thawing as well as temperature changes may result in rapid degradation of 3-OHP causing falsely decreased concentrations of 3-OHP, whereas we found raised concentrations of 3-OHP in the patients with Alport's syndrome.

The increased excretion of 3-OHP may possibly be explained as follow: after ribosomal translation of basement membrane collagen proteins, prolyl residues are subjected to the action of post-translational enzymes such as prolyl hydroxylase, lysyl hydroxylase, glycosly transferases, etc. There is a highly specific 3 and 4 prolyl hydroxylase acting only upon non-helical collagen proteins. Cross linking and helical formation of collagens are possibly disturbed in Alport's syndrome.[17] Therefore non-helical collagens could be subjected to a prolonged action of post-translational enzymes, possibly preferably to 3-prolyl hydroxylase. This could lead to an increased excretion of 3-OHP whereas other basement membrane amino acids such as 4-OHP and hydroxylysine would be excreted in normal amounts (see above).

The high specificity and sensitivity of the increased 3-OHP excretion in patients with Alport's syndrome suggest that the determination of 3-OHP could be helpful as a screening test for this disease, especially if the noninvasiveness, simplicity, and specificity of the method is taken into consideration. Further studies are needed to confirm its clinical relevance.

We are highly indebted to Dr J Häusler, Institute of Organic Chemistry, University of Vienna, for the synthesis of the structural analogues. We also highly appreciate the excellent technical assistance of Dr M T Weiss and Mrs Dalisay Ronquillo.

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Corrosive injury to the oesophagus

Early oesophagoscopy to assess the presence or extent of damage is now routine after caustic ingestion.[1] There has been doubt about the effectiveness of steroid drugs given to prevent oesophageal stenosis from the more severe injuries.

A trial done in Washington DC (Anderson *et al*, *New England Journal of Medicine* 1990;**323**:637–40) has shown no benefit from steroids given within 24 hours of the ingestion. A total of 131 children were assigned randomly to receive no treatment or steroids, initially given as intravenous prednisolone and later as oral prednisone for a total of five or six weeks. Ampicillin was given concurrently with the steroid.

Oesophageal stricture developed in 10 of 31 children in the steroid group and in 11 of 29 untreated. Four steroid treated children and seven controls needed oesophageal replacement. Neither difference was statistically significant.

ARCHIVIST

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45,X/46,X dic (Y) mosaicism in a phenotypic male

P J Batstone, M J W Faed, R T Jung, J Gosden

Abstract

Cytogenetic analysis, confirmed by in situ hybridisation studies, showed a mosaic 45,X/46,X dic (Y) (q12) karyotype in a 14 year old boy who was initially diagnosed as having Noonan's syndrome. He made an early response to recombinant growth hormone; this suggests that this treatment may improve final height.

The phenotypic expression of Noonan's syndrome and Turner's syndrome is similar and it is important to distinguish between them because of management and counselling. We present a teenage boy who was initially diagnosed as having Noonan's syndrome.

Case report

The boy was born at 41 weeks' gestation with a weight of 2500 g and length 48 cm. At the age of 4 years, his height was recorded as 87 cm (standard deviation score (SDS) −3·4) and at the age of 8·7 years as 109·5 cm (SDS −3·3). At the age of 13·1 years his height was 123·9 cm (SDS −4·3), weight 31 kg, and mean parental height 165 cm. He had a dysmorphic appearance with coarse skin, increased elbow carrying angle, webbed neck, widened nipple distance, and gaps between incisors. There was no shortening of the metacarpals, no audible heart murmur, and normal blood pressure. Axillary and pubic hair were absent, and his genitalia were Tanner stage 2 with testes 3 ml (left) and 5 ml (right) in volume.

Endocrine investigations showed normal thyroid and adrenal function and prolactin concentration. His testosterone concentration was 1·5 nmol/l, follicle stimulating hormone undetectable, and luteinising hormone 6 IU/l. There was a growth hormone peak of 20 µg/l during sleep and a rise with insulin hypoglycaemia to 13·3 µg/l (glucose nadir 2·1 mmol/l).

His growth velocity was 3·4 cm/year (SDS −3·0) before starting treatment with recombinant growth hormone. After 10 months' treatment (4 units five times a week for eight months then 4 units seven times a week) his growth velocity increased to 7·5 cm/year (SDS −1·4). At 14 years of age his bone age by the Tanner-Whitehouse 2 method was 12·4 years. He subsequently went abroad.

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CYTOGENETICS

Chromosome analysis of trypsin/Giemsa banded preparations of cultured lymphocytes from the patient showed the presence of two cell lines. Approximately 40% of cells had a 45, X chromosome constitution while the remainder had 46 chromosomes, apparently with a Y chromosome (see fig 1). In a proportion of cells a second constriction in the Y chromosome was noted. C and Cd banding was performed and two dark staining bands and two pairs of centromeric dots respectively were seen in some cells. Quinacrine staining showed that the usually brightly fluorescent distal heterochromatic region of the Y chromosome was absent in all cells examined.

To confirm that the chromosome was indeed derived from the Y, presumed because the patient was phenotypically male, we undertook in situ hybridisation studies on metaphase spreads using the DNA probes pDP105 and pHY2.1, which map to the juxtacentromeric

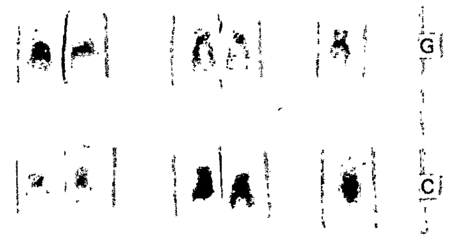

Figure 1 Trypsin/Giemsa (G) and C banded (C) partial karyotypes showing chromosomes 21, 22, and abnormal Y (from left to right).

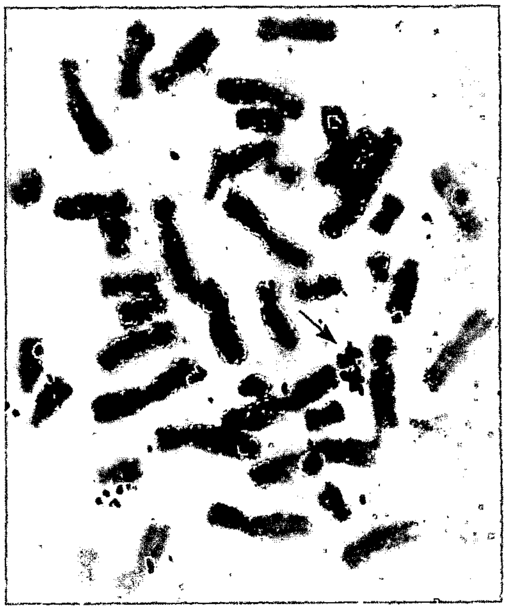

Figure 2 Autoradiograph of in situ hydridisation with DNA probe pDP105 on a metaphase spread from the patient. Note two clusters of silver grains over the abnormal Y chromosome (arrowed).

region of the Y chromosome and to the distal heterochromatic region respectively. In situ autoradiographs showed two clusters of silver grains over the dicentric chromosome with probe pDP105 (fig 2) and none with probe pHY2.1. The karyotype was thus interpreted as 45, X/46, X dic (Y) (pter → q12:q12 → pter).

Parental blood samples were not available.

Discussion

The similarity between the phenotypic expression of Noonan's syndrome and Turner's syndrome can lead to confusion. The familial occurrence of Noonan's syndrome would indicate a dominant mode of inheritance for this condition and the coincident appearance of neurofibromatosis I in some cases may indicate that the Noonan's syndrome gene is also on chromosome 17.

The presence of features similar to those of Turner's syndrome in a phenotypic male specifically provokes a diagnosis of Noonan's syndrome. Some of these phenotypic males, with varying degrees of virilisation, have, however, been shown to be more appropriately called male Turner's syndrome, resulting from the presence of 45, X/46, XY mosaicism. Like the case reported here several of these have shown a non-fluorescent Y chromosome and it has been suggested that they may be dicentric chromosomes derived by sister chromatid reunion in band Yq1.[1] The expected mitotic behaviour and unstable nature of such a dicentric chromosome would predispose to the development of a 45, X cell line resulting, in some cases, in the stigmata of Turner's syndrome.[2 3]

We have been able to show in our case that the Y chromosome present, although not easily distinguishable from a normal Y on conventional trypsin/Giemsa banding, indeed did prove to be dicentric and to have lost the whole of the heterochromatic portion of the long arm when examined by C banding, Cd banding, and quinacrine fluorescence. This was confirmed by use of Y chromosome DNA probes that showed loss of the heterochromatic region recognised by the probe pHY2.1 and duplication of the region near the centromere recognised by the probe pDP105.

Although we were not able, probably for technical reasons, to demonstrate two centromeres in all cells no Y chromosomes with normal heterochromatin were observed. Unfortunately we were not able to examine the paternal chromosomes but the father was reported to be of normal phenotype.

It is clearly important from management and counselling aspects to ensure that Noonan's syndrome and Turner's syndrome are distinguished in patients. The latter are at risk of gonadoblastoma when Y chromosomal material is present and the reproductive expectations and recurrence risks are different for the two syndromes.

It has been suggested that gonadoblastoma is less likely to develop in dysgenic gonads when the Y chromosome lacks the fluorescent region.[4] The number of cases for which long term surveillance is available and which contribute to this conclusion is small, however, and there should be caution in adopting a policy of non-interference. In males with descended testicles, such as this case, long term observation of the testes should be feasible.

Recent evidence in the use of recombinant growth hormone in female patients with Turner's syndrome has indicated the beneficial effect of this treatment in improving growth velocity and final height.[5] The initial response to growth hormone in our patient suggests that such treatment may also have an important role in treatment of males with this syndrome.

We thank Sandra Reid and Sharon Mudie and are grateful to Professor Bonnici at Groote Schuur Hospital, Cape Town for his initial assessment and subsequent referral.

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Congenital parvovirus infection

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Abstract

A case of congenital parvovirus (B19) viraemia with associated thrombocytopenic purpura and platelet antigen incompatibility in an infant is reported. Results of laboratory investigations indicated that the baby was infected in utero.

A recent report has shown evidence of the sequelae of congenital parvovirus (B19) infection.[1] Others have shown haematological consequences of infection in an otherwise normal infant.[2] We report a confirmed intrauterine infection with B19 in an infant, which was associated with thrombocytopenic purpura and platelet antigen incompatibility.

Case report

An infant boy was born at 37 weeks' gestation after a normal delivery. Pregnancy had been

Investigations for parvovirus B19

	Time sample taken after birth	*B19 IgM**	*B19 IgG**	*B19 DNA†*
Mother	2 weeks	>100	35	Negative
	8 weeks	31	>100	Negative
Baby	Birth	33	6·1	Positive
	2 weeks	>100	6·5	Negative
	8 weeks	6	19	Negative

*Radioimmunoassay units: <1 negative, 1–3 equivocal, and >3 positive.
†Dot blot hybridisation assay with digoxigenin labelled probe.

uneventful with no evidence of maternal illness. He weighed 2600 g and his Apgar scores were 8 at birth and 10 at five minutes. Three hours after birth the infant was noted to have a widespread petechial rash over his trunk, limbs, and palate and larger bruises were evident over bony prominences. There was no hepatosplenomegaly and examination was otherwise unremarkable. Initial investigations showed a haemoglobin concentration of 169 g/l, white cell count $20{\cdot}7\times 10^{9}$/l (74% neutrophils), and platelets $19{\cdot}0\times 10^{9}$/l. Clotting screen and bacterial infection screen were normal. Recovery was uneventful except for moderate jaundice requiring four days of phototherapy. By day 8 the platelet count was 550×10^{9}/l. Cranial ultrasound scan was normal.

Further serological investigation showed the father to be platelet antigen (Pl^{A1}) positive and the mother Pl^{A1} negative. The mother also demonstrated anti-Pl^{A1} antibody. The infant was Pl^{A1} positive and his serum cross reacted with that of his mother.

Discussion

The results of B19 investigations (table) indicated intrauterine infection with a high concentration of specific IgM and a rising concentration of specific IgG in mother and infant. In addition DNA studies demonstrated a viraemia in the first infant sample that cleared as the IgM rose. The recent survey by the Public Health Laboratory Service on B19 in pregnancy suggested a 30% intrauterine infection rate but no case showed the presence of the viraemia in the infant and no thrombocytopenia was noted.[1] A recent report showed viraemia in a 2 month old infant but this was persistent and associated with erythroid hypoplasia.[2] Maternal infection was not reported in this case. Others have demonstrated antiplatelet antibodies and thrombocytopenic purpura in previously normal children with viral infections, including parvovirus.[3 4] This case shows not only confirmed intrauterine infection with B19 and transient viraemia in the newborn infant, but the association with thrombocytopenic purpura and platelet antigen incompatibility; this has not previously been demonstrated with congenital parvovirus B19 infection.

We would like to thank Dr R Greenham for allowing us to report this case and Dr JE Cradock-Watson (Public Health Laboratory, Manchester) for his help.

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REJOINDER

Blue breath holding is benign

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Southall *et al* described 51 infants and young children with recurrent episodes of cyanosis and loss of consciousness of whom 'eight died suddenly and unexpectedly'.[1] The authors alleged that 'these cyanotic episodes [which] included both intrapulmonary shunting and prolonged expiratory apnoea . . . are a cause of sudden unexpected death in infancy and early childhood'. Many readers will have inferred that the message of this article is that blue breath holding attacks carry a mortality, indeed a mortality of 16%.

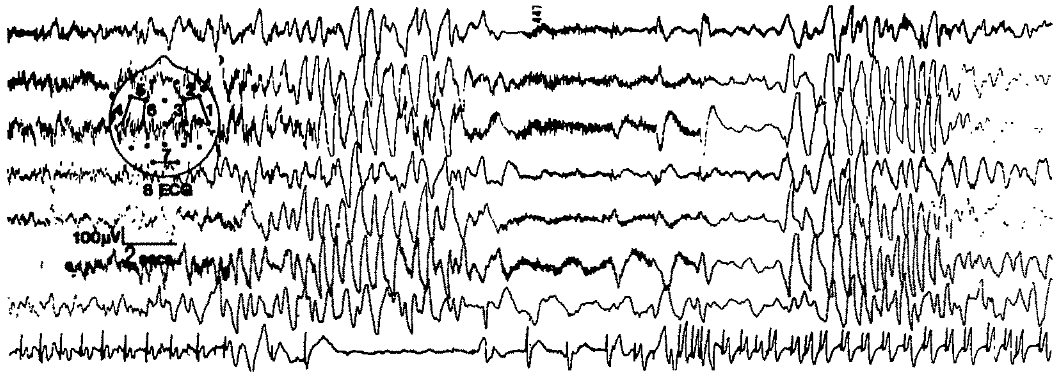
I have recently had the opportunity to review the clinical features and mechanisms of the many syncopes and anoxic seizures that afflict the young.[2] In terms of outcome, these tend to fall into one of two groups, the hazardous and the benign. First there are those fits or faints in which a treatable component should be recognised by the doctor to avoid a substantial risk of brain damage or death. Examples include those anoxic seizures induced by forcible smothering[3] and those associated with ventricular tachyarrhythmias or sick sinus syndrome. Secondly there are those syncopes in which a negative feedback or fail safe mechanism normally operates, with automatic recovery however horrific the episode appears to the observer. Here, the doctor's main function is to provide reassurance and dissolution of parental anxiety. In this benign group I have placed breath holding attacks (cyanotic and 'mixed')[2] (52 59) and so called 'reflex anoxic seizures'[2] (69 92) (previously called 'white breath holding' attacks[4]). Indeed, the cornerstone of management of breath holding spells is that one says to the parents that *these attacks will not do harm*,[5] echoing well established opinion.[6 7]

Southall *et al* appear to have reached fundamentally different conclusions.[1] The writer of one editorial has interpreted their data as demonstrating a 15% mortality in a disorder perceived as similar to but not identical to breath holding.[8] It is therefore important to determine first whether the patients reported in the papers of Southall *et al* did have breath holding spells as usually understood, and if so whether their paper contains the scientific basis for breath holding spells having a high mortality and being a mechanism for sudden infant death.

Is breath holding the subject matter?

Southall *et al* specified that 'In all 51 patients most of the cyanotic episodes began when the child was awake, usually after a naturally occurring stimulus such as pain, fear or anger resulting in a cry or an attempt to cry . . . . Episodes commonly began with a series of expiratory cries without inspiratory efforts, often with a widely open mouth. Sometimes an episode began with a single prolonged cry that was silent, the expiratory apnoea beginning immediately'.

The authors stated that such episodes 'have been previously described as cyanotic breath



Ambulatory cassette recording (seven channel EEG, one channel ECG) of a breath holding spell. Time calibration bar on left of figure is two seconds. The slow–flat–slow appearance on the EEG indicates severe cerebral hypoxia. This begins at maximum forced expiration, coincident with the onset of eight seconds cardiac asystole. The asystole is neither a consequence of the hypoxia nor the cause of the EEG flattening, but reflects a strong simultaneous vagal discharge. 'Intrapulmonary shunting' is presumably minimal during such a cardiac standstill.

The figure is reproduced with permission from 'Fits and faints' by J B P Stephenson, published by Mac Keith Press/Blackwell Scientific, 1990 (see pages 47–54 and figure 7·8).[2]

holding attacks', with a 'presentation . . . identical to that described as "cyanotic breath-holding" ',[1] but as some have doubted this identity[8] I have sought further clarification. During a recent scientific meeting (Scottish Cot Death Trust SIDS Research meeting, Royal College of Physicians and Surgeons of Glasgow, 28 November 1990) Dr David Southall agreed that the patients he was talking about had *identical* cyanotic episodes to those which I had recorded on videotape.

This videotape was of two typical breath holding spells in a 15 month old girl as illustrated in the figure. To make this meaningful to the clinical reader, the history is briefly summarised:

Breath holding spells began aged 7 months, five days after diphtheria, pertussis, and tetanus immunisation. Their frequency varied from two to six or more daily. Rarely there had been two days without spells, but more usually the interval was two hours. Provocations included being frightened or her mother going out of the room, but were not always obvious. The parents' description was 'starts to cry, doesn't really cry, no cry come out, goes blue bluey-red darkish, stiffens up arms out straight, head back, unconscious'. Because some of these breath holding spells were followed by rhythmic limb twitching for up to three mintues ('anoxic-epileptic' seizures,[2 (112 135)] videorecording and cassette electroencephalography (EEG)/electrocardiography (ECG) recording was undertaken. A total of 15 spells were recorded, all anoxic rather than anoxic-epileptic. Continuous rapid (3 per second) expiratory grunting led to rapid cyanosis and opisthotonus with EEG flattening within 40 to 45 seconds. Vocalisation was then followed by a stare and chewing while the EEG showed high voltage slow waves; alertness returned about 70 seconds after onset. The ECG showed bradycardia with asystole of 2–8 seconds beginning just before first signs of hypoxic EEG change, but this had no obvious additional effect on the clinical or EEG changes and atropine did not prevent the appearance of the spells in their usual form. Ocular compression induced simultaneous 2–3 per second expiratory gasping and asystole for 7 seconds, with no obvious loss of consciousness and only minor EEG slowing (2–2·5 cycles per second for 4 seconds). At the age of 2·5 years spells continued at the same rate, but the parents did not wish treatment. The child showed strong personality and good intelligence.

Is cyanotic breath holding dangerous?

In a previous paper Southall *et al* state: 'The rapid onset of severe hypoxaemia suggest[s] that this form of apnoea [cyanotic breath holding] may be an important cause of sudden death . . . . the fact that none of the subjects reported here has died leaves the relation to SIDS open to further investigation'.[9]

This recent paper provides no scientific support for the suggestion that there is an excess of sudden unexpected death in those with prior breath holding spells.[1] There is no means by which the reader can tell from what population the 51 infants and young children who form the subject matter originated. Of the four children who are said to have died in a cyanotic attack, one had a repaired tracheo-oesophageal fistula, one a cleft palate, and the remaining two suffered developmental delay and (iatrogenic) tracheostomy. Of these two latter children one (case 23) must surely have had *primary* progressive cerebral atrophy (but the neuropathology is not reported), and the details of the other (case 18) are totally inadequate. As the only case in which extraordinary intrapulmonary shunting is suggested by the very limited evidence provided, case 18 surely must be published in full.

Four additional boys are cited as having died suddenly and unexpectedly after earlier typical breath holding attacks. One was found to have a brainstem glioma.[10] In the remaining three, there are no population data or other way of knowing whether this coincidence was improbable, that is, not expected by chance. My only surprise is that more examples were not discovered.

There is a potential second hypothesis (not explicitly introduced in the opening to the article by Southall *et al*[1]) that a novel form of intrapulmonary shunting is the basis of cyanotic breath holding spells, but is not clear why their results cannot be explained by a combination of low lung volume and rapid oxygen consumption.[11 12]

A third hypothesis, combining these two, is that intrapulmonary shunting is a mechanism for sudden death. As I have alluded to above, the terminal events in case 18 seem to bear precisely on this question. Adequately documented details would allow the reader to judge this issue.

Literature review

Southall *et al* appear to ignore the extensive studies on breath holding spells undertaken by the authors of yesteryear, whether on prognosis[6 7] or regarding mechanism.[11 12 13] The extensive studies of Gastaut[2 (187 8) 14] receive no mention. No consideration is given to the observation that apparently vagal mediated asystole may occur in a child who also has cyanotic breath holding on other occasions,[6 7 13] nor to the observation that vagal asystole may also be a part of so called 'mixed' breath holding, as in the figure.

Clinical criticisms

The authors clearly believed the parents that their children's episodes were life threatening, and the death of a number of children would bolster that belief: 'Investigations . . . and uncontrolled trials of treatment were considered essential . . . the *need for resuscitation* [my italics], and ethical concerns limited the information that could be collected'.[1] It is a difficult and delicate area in which to venture (the more so with the authors' dedication to four of the children) but the question has to be asked, if the prognosis was worse than expected from previous studies, whether any aspect of management might have tilted the balance in an adverse direction. It has long been known that tracheostomy does not prevent cyanotic breath holding.[12]

Future studies

I am not convinced that Southall *et al* have demonstrated an excess mortality from breath holding spells in otherwise healthy children. None the less hints of autonomic disturbance may deserve further study,[8 15 16] provided investigators—even in the face of daily and severe attacks—can withstand the temptation to 'resuscitate' or give uncontrolled treatments.

Insufficient attention has been paid to the neurological basis of the active expiration which is an essential feature of breath holding attacks, but which may also be seen in those pallid syncopes (associated with cardiac asystole) induced by ocular compression in the laboratory.[13] Obviously the oculorespiratory reflex is no more involved in natural breath holding than is the oculocardiac reflex in those 'reflex anoxic seizures' mediated by cardiac asystole, but it can be studied safely and ethically[17] and it is not confined to man. What is self evident is that if continued brainstem neuronal drive is necessary to inhibit active inspiration and/or cardiac systole, then sufficient hypoxia and/or ischaemia must reverse this inhibition.

Summary

In their recent publication in this journal, Southall *et al* described typical cyanotic breath holding spells, both in otherwise healthy children and in those with brainstem lesions and other malformations.[1] Their suggestions regarding possible autonomic disturbances may require further study, but they have adduced no scientific evidence to contradict the accepted view that in the intact child blue breath holding spells are benign.

Those families in which an infant suffers an 'apparently life threatening event' deserve immense understanding and help, and it behoves investigators to exercise extreme care and self criticism in the presentation of new knowledge which may bear upon their management and their morale.

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Cyanotic 'breath holding' and sudden death

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Dr Stephenson raises an important issue concerning the risk of sudden death during cyanotic breath holding. Our recent paper describes investigations to understand further the *pathophysiological mechanisms* responsible for severe cyanotic breath holding and did not attempt to estimate the risks of this disorder.[1] To do this would require a population based study, ideally prospective in nature, in which there was almost complete follow up. The historical studies mentioned by Dr Stephenson are unable to confirm that no deaths occurred. Thus in the study of Laxdal *et al*[2] and Lombroso and Lerman,[3] 18% and 43% respectively were lost to follow up. One possible reason for a lack of response to posted questionnaires might have been the death of a child.

We trusted that readers would not automatically infer from reading our paper that there is mortality of 16% in cyanotic breath holding. As stated, our patients were at the severe end of the spectrum and therefore not representative of the whole population of 'breath holders'. Furthermore, Hunt in his recent editorial did not claim that 15% of breath holders die, but was specifically referring to our collection of patients.[4] Our cases were 'selected' by virtue of their referral to us by their paediatrician who, with the parents, was concerned about the severity of the hypoxaemic episodes.

Dr Stephenson omits to mention our own prospective population based study of sudden deaths between 1 and 5 years of age.[5] This involved the follow up of 9856 infants all of whom were tagged for future death by the Office of Population Censuses and Surveys. Two of the deaths between 1 and 5 years in these 9856 children occurred during cyanotic breath holding. Based on Lombroso and Lerman's estimated incidence of cyanotic breath holding as 2·8% of all children,[3] around 276 of our 9856 cohort should have suffered from this disorder. Thus around two of 276 or 0·7% of children with cyanotic breath holding are likely to have a fatal outcome. If one can accept a 0·7% mortality rate, statements concerning the benign nature of this condition are correct.

There are three other reasons why we consider that the *severe* forms of cyanotic breath holding are not benign. Firstly unconsciousness is due to severe cerebral hypoxia and this is recognised as a cause of cerebral injury. Secondly our discussion with older children experiencing these episodes suggest that they are an unpleasant experience: children describe an inability to breath in and a feeling of suffocation. Finally, severe episodes frighten not only parents, but also experienced nursing and medical staff, who cannot accept that they are benign. The appearances of a child apnoeic, cyanosed, unconscious, developing rapid and profound bradycardia, does not appear compatible with a condition described as benign.

The rapid onset of severe hypoxaemia (falls in arterial oxygen tension to 2·1–3·9 kPa in 10 to 25 seconds) cannot be explained simply by low lung volume and rapid oxygen consumption. Although prolonged expiratory apnoea is the most frequent accompanying respiratory abnormality, we also reported that 'severe hypoxaemia may develop rapidly despite continued spontaneous or mechanical ventilation'. Hence we searched for a right to left shunt of desaturated, mixed venous blood. It was impossible for all patients to undergo all of the investigations necessary to confirm the development of an intrapulmonary shunt, but episodes in all 51 of our patients were in all other respects similar to those occurring during krypton infusion scans and contrast echocardiography.[1]

We do not advocate tracheostomy, which does not prevent episodes and by disabling laryngeal control may be detrimental. The tracheostomies in the patients who died were inserted before referral in order to ease resuscitation. We were also wary about commencing any medication and none of our eight cases who died was being treated with tetrabenazine or clonidine. However, when a child is having to be artificially ventilated using a bag and face mask several times each day (and we can reassure Dr Stephenson that this was required to avoid endotracheal intubation), then search for an effective treatment was considered ethical. We are now conducting a randomised, double blind, crossover trial of clonidine.

Dr Stephenson claims that insufficient attention was given to the 'neurological basis of the active expiration'. We did, however, discuss and reference studies where, for example, infusion of noradrenaline onto brainstem neurones produced apnoea. Recent work by Kaada reinforces our view that emotional responses may have profound effects on cardiovascular and respiratory reflexes.[6] Dr Stephenson's figure is reported to show cerebral hypoxia with cardiac asystole. However, the recording does not illustrate oxygen or breathing signals; the reported cardiac asystole may be due to loss of electrode contact.

Dr Stephenson also implies that we should not have interfered with the natural history of episodes by attempting resuscitation. For the majority of young children with isolated and infrequent episodes we would agree with this opinion. However, for those with frequent episodes involving loss of consciousness, we consider Dr Stephenson's advice to be inappropriate; eight of 51 such cases reported in our paper died. Since our publication we have experienced an additional case which highlights the danger of adopting a conservative approach to the management of patients at the worst end of the spectrum of this disorder:

> This infant presented at 6 weeks of age with severe hypoxaemic episodes which were clinically recognised as cyanotic breath holding. Investigations in our department confirmed the presence of active expiratory 'apnoea' and intrapulmonary shunting. His parents were given a transcutaneous PO_2 monitor to identify any episodes that should occur when he was not being observed. His episodes had always occurred when he was awake and his mother did not believe that they would occur when he was sleeping. Nevertheless the episodes were considered by us and his referring paediatrician to be extremely dangerous and it was explained to his mother that an episode might occur if he awoke from sleep and became frightened or angry. One afternoon at the age of 10 months, he was settled to sleep in his cot (unattached to the oxygen monitor). Forty five minutes later his mother found him dead. A postmortem examination showed patchy congestion in the lungs with some milk in the larger airways; these findings were reported to be compatible with sudden infant death syndrome, although, because of his previous history, his death was certified as due to 'apnoea of infancy'.

In summary, the episodes of hypoxaemia described in our paper represented the severest form of cyanotic breath holding (a term which is unfortunate in that it implies a voluntary component). A functional disturbance, which involves intrapulmonary shunting and prolonged expiratory apnoea, represents the best explanation for the final pathophysiology leading to the sudden and unexpected deaths that occurred in eight of our 51 patients, despite the pathology found in some at postmortem examination.[7] The risk of sudden death in all patients with clinically recognised cyanotic breath holding appears to be very low, but we would continue to be concerned by episodes in infants less than 6 months of age or in those with frequent loss of consciousness. The identification of an effective treatment will not only help in our understanding of the mechanisms responsible for these episodes, but may also improve the lives of many young infants and their families.

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PERSONAL VIEW

Is Asperger's syndrome a useful diagnosis?

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The first published account of early infantile autism was in 1943 and Asperger's original paper appeared the following year.[1] Childhood autism and Asperger's syndrome are in many ways similar and there is continuing argument as to whether it is useful or appropriate to consider them as separate entities.[2, 3]

In the 9th revision of the *International Classification of Diseases* (ICD-9) infantile autism is a subcategory of psychoses with origin specific to childhood and Asperger's syndrome is not a listed subcategory (see table 1).[4] The revised American classification in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III), considered that infantile autism was no longer appropriately classified with psychoses and included it as a subcategory under the general classification of pervasive developmental disorders.[5–7] Again there is no separate subcategory for Asperger's syndrome. Pervasive developmental disorders are seen as characterised by a qualitative impairment in the development of reciprocal social interaction and of verbal and non-verbal communication skills, autistic disorder being the one acknowledged specific subcategory. Field trials have shown that there are two mandatory criteria for autistic disorder: an appreciable lack of awareness of the existence or feelings of others, and persistent preoccupations with parts of objects.[8] Gillberg has criticised the use of the term pervasive developmental disorder preferring 'autism spectrum disorders' and he has recently suggested that a separate diagnostic designation of infantile autism doesn't seem to make a 'lot of sense any more'.[9] Although he argues that the term 'pervasive developmental disorder' is too loosely defined and that the disorders included in the category are 'specific' and/or 'partial' rather than pervasive, it seems likely that there is no intended difference in the range of disorders covered by the term 'pervasive developmental disorder' and 'autism spectrum disorder'.

Despite Gillberg's criticisms and sceptism about subclassification, the 10th revision of the *International Classification of Diseases* (ICD-10) is adopting the term, pervasive developmental disorders, and includes subcategories not only of childhood autism but also Asperger's syndrome (see table 2).[10] How is it proposed that this diagnostic term is to be used? It is useful? It appears that Gillberg uses Asperger's syndrome as the equivalent of 'high functioning autism'.[9] If that is really how the term is to be used, then one may indeed wonder whether it is appropriate to have a separate subcategory. In his original description, Asperger emphasised a number of features.[1, 11] Firstly, the child usually begins to speak at the age expected in normal children and a full command of grammar is sooner or later acquired. However, the manner of speaking is often pedantic and subjects engage in monologues rather than conversations. Use of gestures tends to be restricted and comprehension of others' facial expressions and gestures is poor. Secondly, there is an impairment of two way social interaction with a lack of ability to understand and use the rules governing social behaviour. It appears that there is not a primary desire to withdraw from social contact, rather a lack of ability to comprehend social situations and respond appropriately. Thirdly, as in infantile autism, there is commonly in early childhood a preoccupation with particular activities and resistance to change. Later there are all absorbing circumscribed interests and engagement in routines. Fourthly, gross motor movements are characteristically clumsy and uncoordinated.

It will be seen that the description of Asperger's syndrome is substantially similar to the picture in some relatively intelligent individuals with a diagnosis of infantile autism. Indeed, Asperger originally believed that people with his syndrome were of high intelligence. What stands out as different from infantile autism is the superficially normal early language development. The term, Asperger's syndrome, therefore proposes that there are a group of

Table 1 International Classification of Diseases, 9th revision

299	*Psychoses with origin specific to childhood:*
1·0	Infantile autism
1·1	Disintegrative psychosis
1·8	Other
1·9	Unspecified

Table 2 International Classification of Diseases, 10th revision

F84	*Pervasive developmental disorders:*	
F84·0	Childhood autism	
F84·1	Atypical autism	
	F84·10	Atypicality in age of onset
	F84·11	Atypicality in symptomatology
	F84·12	Atypicality in both age of onset and symptomatology
F84·2	Rett's syndrome	
F84·3	Other childhood disintegrative disorder	
F84·5	Asperger's syndrome	

individuals who have a disorder of social development similar to that found in infantile autism, but with a pattern of early language development that appears grossly normal; at least as regards the milestones that are usually recorded. Tantam states that there is no difficulty with propositional language but 'marked pragmatic impairment'.[3] The core features of autistic social development are often referred to as 'Wing's triad': deficits in social interaction, communication, and imagination.[12]

A major diagnostic difficulty in infantile autism is that the classical criteria are most easily recognised among children aged between 3 and 5 years. It is at this stage of development that aloofness and indifference in social interactions may be most readily observed alongside a lack of language, including a lack of comprehension of speech and repetitive physical activities. The pattern of symptomatology changes, however, and changes most noticeably among more able individuals.

Wing has described what she calls an 'autistic continuum' (table 3) in which the most severely disabled individuals are aloof and indifferent in social interaction, the more able or least handicapped characterised by bizarre one sided social approaches.[13] More able autistic individuals who develop language move from no language at age 3 to quite extensive use of speech which, as in Asperger's syndrome, is used in a grammatical but one sided and literal fashion. The suggestion is that there are parallels in function in the areas of social interaction, communication, and obsessional interests and activities. Those of low ability, or those of higher ability at an earlier stage of development show aloofness, no language, and simple repetitive activities. More able individuals, particularly at a later stage of development, display a more elaborate picture of social ineptness, circumscribed interests, and concrete egocentric use of language. This analysis could be seen to reinforce the notion that Asperger's syndrome is no more than high functioning autism. There are individuals, however, with autistic social development who have appreciably abnormal early language development including a significant delay in comprehension of speech, who subsequently attain to a high functioning picture. There are others, also high functioning, who do not have a history of abnormal early language development, at least in a gross sense.[14]

Does this matter? If it is true that a similar high functioning autistic picture can be obtained on the basis of quite different early language development, what are the implications for our understanding of the relationship between social and language development? It may be that there are subtle or not so subtle differences among the high functioning 'autistic' individuals with these discrepancies in early language development. For example, it has been suggested that those with superficially normal early language development speak spontaneously more often and demonstrate an active, if restricted fantasy life (S Wolff, personal communication).

It is just this difference in early language development that is used as a basis for the establishment of the subcategory of Asperger's syndrome in ICD-10. It states that in Asperger's syndrome there is 'A lack of any clinically significant general delay in language or cognitive development'.[10] The criteria for qualitative impairments in reciprocal social interaction are identical with those for childhood autism. The same is true for the restricted, repetitive and stereotyped patterns of behaviour, interest, and activities. However, it is commented that it would be 'less usual for these to include either motor-mannerisms or preoccupation with part objects or non-functional elements of play materials'. The aim appears to be to draw attention to the existence of children with social developmental disorders of a type found in childhood autism but without a major disorder of language development affecting comprehension and expression.

There may be an empirical descriptive basis for a diagnosis of Asperger's syndrome, but there does not appear yet to be any definite psychopathological nor neuropathological distinction from high functioning childhood autism. A recent study of the use of intonation to communicate, however, which compared subjects with Asperger's syndrome with high functioning autistics concludes that 'an early history of deviant language' 'is associated with more pronounced failure to use intonation to communicate effectively later during childhood and adolescence' (A J Fine *et al*, unpublished observations). There were also differences in the ability to decode non-verbal social information.[15]

Considerable progress has been made in trying to understand the nature of the psychological processes which are dysfunctional in childhood autism. Two main views are, on the one hand that there is a deficit in the innate ability to interact emotionally with others, and on the other an impairment in the cognitive process of metarepresentation.[16] [17]

The ability to form representations of representations is considered necessary in order to 'mentalise'—that is, to think and reason about one's own and others' minds. Attribution of beliefs and intentions to others is said to reflect an individual's 'theory of mind'. Communica-

Table 3 The autistic continuum (features most often used in diagnosis)[13]

Item	*Tend to be seen in the most severely handicapped/retarded*			*Tend to be seen in least severely handicapped/retarded*
Social interaction	(1) Aloof and indifferent	(2) Approaches for physical needs only	(3) Passively accepts approaches	(4) Makes bizarre one sided approaches
Social communication (verbal and non-verbal)	(1) No communication	(2) Needs only	(3) Replies if approached	(4) Spontaneous, but repetitive, one sided, odd

tion that is not modified by inferences about other's beliefs and intentions is literal and one sided.[18]

The metarepresentational deficit theory has been criticised on the ground that deficiencies in joint attention behaviour are a feature of autistic children and that these normally emerge between 6 and 9 months of age, at least six months before the capacity for metarepresentation.[19]

Further criticism comes from the other main theory that argues that the exclusively cognitive formulation of the metarepresentational hypothesis misunderstands the connection between social and emotional development.[20 21] Hobson suggests that autistic individuals fail to develop an adequate concept of persons because 'an impairment in biologically based capacities for engaging in (and representing) personal relatedness, especially affective relatedness'. This impairment is present before the stage at which joint attention usually develops.

This second main view has in turn been attacked on the ground that there is no empirical support for the hypothesised affective disorder in infancy.[22] In addition, recent work suggests autistic children can develop selective attachments and that they also pick up the feelings of others.[18 23] Sigman and Mundy regard the children's difficulties as one of social comprehension—the identification of the significance and meaning of their experiences—rather than one of social responsiveness.[23]

The various theories are concerned with a social psychological deficit that is conceived as a core dysfunction in both autism and Asperger's syndrome. If the underlying dysfunction is detectable before language develops then the level of deficit could be comparable in the two conditions when individuals are matched for intelligence quotient and language level. If the core dysfunction lies in metarepresentation, however, it could be expected to be alleviated in those whose language development is relatively preserved. In other words it would be predicted that those with Asperger's syndrome would have better empathy than those with autism. Whether this is so is not known.

Although there is increasing evidence of neuropathology among autistic children,[9] and a wide variety of specific pathologies may underlie the manifestation of the syndrome, there is still considerable debate about localisation. Neuropsychological studies do not assist in this respect.[17] Recent investigation by electroencephalography has supported the notion that there may be deficits in information processing (H van Engeland, paper given at European Medical Research Councils workshop; Brussels, November 1989),[24] but it has been proposed that the most consistent recent findings point to brain stem pathology.[9]

From the genetic point of view there is disagreement about the significance of the fragile X anomaly, although a very recent authoritative review states that it is 'now clear that the proportion of autistic individuals with fragile X is no higher and may even be lower than the proportion of mentally retarded individuals with fragile X'.[25] It is further suggested that among individuals with fragile X social anxiety is more characteristic than social indifference and that hyperactivity and attentional problems are extremely common with frequent abnormalities in spoken language. It is nevertheless considered that this genetic anomaly may be important in a small number of individuals with autism. Other evidence supports the overall significance of genetic factors in autism, although there is still some doubt as to the extent to which any of them is specific for the social developmental disorder as opposed to certain cognitive abnormalities.[25 26] It is not evident what the position is with regard to Asperger's syndrome and this is partly because it is unclear whether research into high level autistic children can be considered research into Asperger's syndrome. DeLong and Dwyer found that high functioning autistics have a positive family history for Asperger's syndrome and low functioning autistics have a high incidence of abnormal neurological findings.[27] Bipolar affective illness was also more common among families of high function autistics. This study claims that there was little distinction between high functioning autism and Asperger's syndrome among its probands, but the criteria used for the diagnosis of Asperger's syndrome did not include superficially normal early language development.

With regard to the prevalence of Asperger's syndrome, it has recently been reported to be of the order of 2·6–3 per 1000 children with a heavy male preponderance as in childhood autism.[28] However, the Gillbergs used delayed language development and mild or moderate impairment of language comprehension as *inclusion* criteria for Asperger's syndrome alongside 'superficially perfect expressive language'. These criteria obscure the difference between Asperger's syndrome and high functioning autism. The problem appears to arise from a desire not to assign a diagnosis of autism to individuals with 'superficially perfect expressive language' in adolescence who met criteria for autism at age 3 to 5 years. Nevertheless it must be recognised that there are considerable difficulties in drawing the line between normality and pathology for empathic aspects of social development.

Conclusion and comment

In clinical practice it can often appear a somewhat sterile academic exercise to decide which subcategory of pervasive development disorder is appropriate for a given child. The phrase 'autistic spectrum' is problematic because the abnormalities of development in the different areas do not correlate very exactly. For example, knowledge of a child's general intellectual level does not predict whether they have an autistic social developmental abnormality, although it is of course more common among those with low intelligence. Wing and Gould reported that half of the severely mentally retarded have the 'triad' of impairments in social recognition, social communication, and social understanding.[29] Similarly, a developmental language disorder affecting comprehension does not necessarily predict a major social developmental disorder, although recent follow up has suggested that such children do have some social difficulty, if not of severity that would make a diagnosis of pervasive developmental disorder appropriate.[30]

Although there is a danger that children are assigned to a diagnostic slot because they do not fit, or that disagreement between experts leads to unnecessary confusion for the parents, Asperger's syndrome is, on balance, a useful diagnosis.

There is a clear advantage in selecting specific subgroups such as those with childhood autism or Asperger's syndrome as defined in ICD-10 for research purposes, because it may help disentangle the relationship between different aspects of development. Clinically the diagnosis of Asperger's syndrome is valuable in that it draws attention to the fact that in young children there may be significant abnormalities of social development of autistic type even where other aspects appear relatively normal. In addition the specific diagnostic label can be of use to some parents in helping them come to terms with the nature of their children's disabilities. It can be helpful also in obtaining appropriate resources. Because the different developmental problems do not run in parallel, however, this does not preclude the need to address the specific problems of individual children.[13]

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PERSONAL PRACTICE

Accidental poisoning in children: can we admit fewer children with safety?

J R Sibert, P A Routledge

Accidental poisoning, despite the impact of child resistant containers, remains a common problem. In England and Wales the Home Accident Surveillance System suggests that 36 000 children presented to accident and emergency departments in 1986 (Department of Trade and Industry, 1988, personal communication). Nevertheless most of these children do not have serious symptoms[1] and have either taken a relatively non-toxic substance or not enough of a toxic substance to cause problems. Nevertheless, a few children do die from accidental poisoning,[2] and a few would die without expert medical care. Is it possible to avoid admitting children unnecessarily while still maintaining safety?

Classifying poisons taken by children

We suggest a way round this dilemma in the treatment of accidental poisoning is to classify the substance the child has taken into one of four categories: low toxicity, intermediate toxicity, potential toxicity, or uncertain toxicity. Children who have accidentally taken a substance of low toxicity can be sent home. Children who have accidentally taken a substance of intermediate toxicity can be observed for a short period in the accident and emergency department or paediatric ward. Many accident and emergency departments now have special areas for children where they can stay for periods of time up to a few hours. Alternatively most paediatric wards are able to accommodate children, who are not formally admitted, for short periods of time for observation. Children who have taken a substance with a potential for toxicity should be admitted for observation and treatment. The local poisons information centre should be contacted if there is any doubt concerning the toxicity of a substance or the treatment that is needed.

A suggested classification of substances children take accidentally (including medicines, household products, and plants) is shown in the table. The substances in this table are those most commonly taken by children accidentally and we have chosen them from information from the work of Craft *et al*,[3] Sibert *et al*,[4] and from inquiries to the Welsh National Poisons Unit.

Deliberate and non-accidental poisoning

It is important to differentiate between children who have accidentally taken poisons and those who have either deliberately taken poisons or been poisoned deliberately. Accidental poisoning is a problem with toddlers with a mean age of 30 months. Children who have deliberately taken poison are usually much older than children who accidentally poison themselves and should be easily recognised. They need full psychiatric and social assessment and should be admitted to hospital.[5] Children who have been deliberately poisoned by their parents need admission so that they can be fully assessed both medically and socially.[6] They will also need referral under the local child abuse procedures.

Preventing further accidents

The parents of all children who present with accidental poisoning in childhood should be given advice regarding storage of medicines and household products. The health visitor should be contacted in all cases remembering that family psychosocial stress is often linked with accidental poisoning in childhood.[7] There may be specific problems that need medical or social help.

Accidental poisoning in childhood with substances of low toxicity

Children who have taken substances of low toxicity can be allowed home after assessment. If there is doubt over what a child has taken a conservative approach should be taken. Emptying the stomach is not necessary in these cases.

Which substances can be classified as of low toxicity?

Antibiotics, with certain exceptions such as ciprofloxacin, sulphasalazine, and chloramphenicol, are of low toxicity if taken accidentally by children. Despite this children are not infrequently admitted to hospital with antibiotic 'poisoning'. This is not necessary. Similarly antacids, calamine, and zinc oxide do not cause serious symptoms if ingested by children. Oral contraceptives have a theoretical risk of breast enlargement and withdrawal vaginal bleeding if taken accidentally by children but this must be very rare and does not need treatment. Vitamin preparations are also non-toxic if ingested in children, however care must be taken to see that the preparation does not contain iron.

Children also take a number of household products accidentally. Many of are these are

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Guide to toxicity of substances taken in accidental child poisoning

Low toxicity
Substances that come into this category include:

Medicines
Antibiotics (except ciprofloxacin, sulphasalazine, and chloramphenicol)
Antacids
Calamine
Oral contraceptives
Vitamin preparations which do not contain iron
Zinc oxide creams

Household products
Chalks and crayons
Emulsion paints and water paints
Fabric softeners
Plant foods and fertilisers
Silica gel
Toothpaste
Wallpaper paste
Washing powder (except dishwasher powder)

Plants
Begonia
Cacti
Cotoneaster
Cyclamen
Honeysuckle
Mahonia
Rowan
Pyracantha
Spider plant
Sweet pea

Intermediate toxicity
Substances that come into this category include:

Medicines
Antihistamines (most)
Cough medicines (most)
Fluoride
Ibuprofen
Laxatives
Lignocaine gel
Paracetamol elixir
Thyroxine
Salbutamol

Household products
Alcohol containing colognes, after shaves, and perfumes
Bleach
Detergents
Disinfectants (most)
Mercury thermometers
Nail varnish remover
Paints (oil based)
Pyrethrins
Talc (if not inhaled)
Rat or mouse poison
Window cleaners

Plants
Berberis
Fuchsia
Holly
Philodendron
Mistletoe
Dieffenbachia (dumb cane)

Potentially very toxic substances
Substances that come into this category include:

Medicines
Barbiturates
Benzodiazepines
Carbamazepine
Clonidine
Digoxin
Diphenoxylate (Lomotil)
Iron
Lithium
Mefenamic acid (Ponstan)
Metoclopramide
Mianserin (Bolvidon)
Paracetamol tablets
Phenothiazines
Phenytoin
Quinine
Opiates including codeine and cough medicines containing codeine
Salicylates
Hyoscine
Tricylic antidepressants (including dothiepin and amitriptyline) and monoamine oxidase inhibitors
Theophyllines

Household products
Alcoholic beverages
Acids
Alkalis (including dishwasher powder and denture cleaner)
Camphor and camphorated oil
Cetrimide
Carbon monoxide
Disc batteries
Bottle sterilising tablets
Ethylene glycol (antifreeze)
Essential oils (for example, real turpentine, pine oil, citronella, and eucalyptus)
Methanol
Methylene chloride (paint stripper)
Organochloride insecticides
Organophosphate and carbonate insecticides
Paradichlorobenzene moth balls
Petroleum distillates (white spirit, kerosene, or turpentine substitute)
Paraquat and other weedkillers (phenoxyacetic acids)
Phenolic compounds (that is, some disinfectants)
Slug pellets (metaldehyde)

Plants
Arum lily
Deadly nightshade
Laburnum
Yew

The table is reproduced with permission from 'Accidents, poisoning and sudden infant death syndrome' by JR Sibert and P Davies in *Forfar and Arneil's Textbook of Paediatrics.* 4th Ed. Edited by AGM Campbell and N McIntosh. Churchill Livingstone, Edinburgh (in press).

non-toxic[3] and children who have ingested them can be sent home. Examples are chalks and crayons, emulsion paints and water paints, fabric softeners, plant foods and fertilisers, silica gel, toothpaste, wallpaper paste, and washing powder. The only problem with these substances is ensuring that the child has not taken a similar but more toxic substance—for example washing powder not dishwasher powder (which is caustic). There are also a number of plants children may take that are of low toxicity: begonia, cacti, cotoneaster, cyclamen, honeysuckle, mahonia, rowan, pyracantha, spider plant, and sweet pea. Again the only problem should be one of identification.

Accidental poisoning in childhood with substances of intermediate toxicity

Children who have taken substances of intermediate toxicity accidentally should be observed for a period in hospital (usually up to six hours) until one can be confident that important symptoms are not going to occur. If there are adverse factors, particularly social factors or if large quantities have been ingested, children should be admitted to hospital.

Which substances can be regarded as of intermediate toxicity?

ANTIHISTAMINES AND COUGH MEDICINES (MOST)

Most antihistamine preparations and cough medicines do not cause serious symptoms in the quantities taken by children. There may be drowsiness and anticholinergic effects but these should be obvious after six hours' observation. Drowsiness should usually not need treatment. *Those cough medicines based on codeine should be regarded as potentially toxic.*

FLUORIDE

Children may ingest fluoride tablets or drops used to prevent tooth decay. Fluoride has a rapid action but is seldom toxic in the quantities taken by children. Symptoms include vomiting, nausea, and abdominal pain and should be obvious after six hours' observation.

IBUPROFEN

Ibuprofen and other non-steroidal anti-inflammatory agents seem only seldom to cause symptoms when accidentally ingested by children. Symptoms include gastrointestinal irritation.

LAXATIVES

Serious symptoms after accidental ingestion of laxatives are rare. If diarrhoea occurs it usually occurs quickly and should be obvious after six hours' observation.

LIGNOCAINE GEL

Although local anaesthetics such as lignocaine are toxic in overdose causing convulsions, appreciable amounts of lignocaine gel are very seldom ingested accidentally by children.

PARACETAMOL ELIXIR

Paracetamol elixirs such as Calpol are sweet and sickly in large doses and serious accidental poisoning is very rare. There is hardly enough paracetamol in most small bottles of elixir to cause problems. If a child has taken a paracetamol elixir the stomach should be emptied using ipecacuanha. Blood concentrations should be checked four hours after the ingestion if more than 150 mg/kg has been taken. Treatment is only needed if the serum paracetamol concentration is above the recommended treatment line.[8] In most cases children can be discharged after a period of observation.

SALBUTAMOL

Although salbutamol can cause peripheral vasodilation, hypokalaemia, muscle tremors, and agitation, serious symptoms are rare and should be obvious after six hours' observation.

ALCOHOL CONTAINING PERFUMES, COLOGNE, AND AFTER SHAVE

Craft *et al*[3] and Scherger *et al*[9] found no symptomatic cases in their series. Asymptomatic children can be allowed home after a short period of observation to make certain they do not become drowsy.

BLEACH

Accidental ingestion of household bleach causes many fewer problems than would be expected. Craft *et al* found no cases that had any serious symptoms in their series.[3] Local lesions in the mouth can be treated symptomatically and should be obvious after a short period. In the few cases where there is doubt about the presence of an appreciable oesophageal problem endoscopy can be undertaken.

DETERGENTS (ANIONIC)

Anionic detergents such as hand dishwashing liquid and shampoo are only toxic in large doses. Craft *et al* found no serious cases in their series,[3] although vomiting is said to occur in large doses. Observation for a period should be all that is needed in these cases.

DISINFECTANTS (MOST)

Craft *et al* found no serious cases in their series.[3]

NAIL VARNISH REMOVER (ACETONE)

Craft *et al* found no serious cases in their series.[3] Nausea and vomiting may occur if large amounts are taken but children do not often take significant quantities. Observation for a period should be all that is needed in these cases.

PAINTS (OIL BASED)

Craft *et al* found no serious cases in their series.[3] The only problems that occur, unless the paint has lead in it, are caused by the petroleum distillate base. The stomach should not be emptied. In practice children do not seem to take significant amounts.

PYRETHRINS

These insecticides are not usually a hazard if ingested or inhaled accidentally. The child should be observed for a short period.

RAT OR MOUSE POISON

The common ingredients of rat or mouse poison (warfarin or dichlorolose) are usually non-toxic in the doses taken by children. The exact type of poison should by identified by contacting the local poisons centre and in most cases the child can be sent home after a short period of observation.

If large amounts of warfarin are ingested vitamin K can be used but this is not needed in most cases. Craft *et al* found no serious cases in their series.[3]

TALC

Talc is only toxic if inhaled when it may cause retching and choking. Cases of accidental ingestion need to be observed only for a short period to make certain that appreciable aspiration did not occur.

WINDOW CLEANERS

Craft *et al* found no serious cases in their series,[3] and most types are non-toxic apart from the danger of aspiration. The exact type of cleaner should be identified through the poison's centre and in most cases the child can be sent home after a short period of observation.

PLANTS

Berberis, fuchsia, holly, philodendron, mistletoe, dieffenbachia (dumb cane) all can theoretically cause problems if taken in excess, however they are unlikely to cause problems if ingested accidentally by children. Usually only small quantities are ingested and observation for a short period is all that is required.

Accidental poisoning in childhood with potentially very toxic substances

Children who have taken substances of potential toxicity should be admitted to hospital for observation and treatment. Although most children who accidentally ingest these substances come to no harm, there are clear potential problems with all the substances we have put on this list.

Accidental poisoning in childhood where there is uncertainty of toxicity

If there is any doubt about the toxicity of a substance a child may have taken, the local poison's information centre should be contacted day or night (see appendix).

Some children arrive in hospital having taken unknown tablets or household products. Often discussion with the poisons information service will help. If there is doubt the child should be admitted for observation.

Appendix: telephone numbers of national centres

London:	
Guy's Hospital	071 955 5095 or 071 635 9191
Edinburgh:	
Royal Infirmary	031 229 2477
Cardiff:	
Llandough Hospital	0222 709901
Belfast:	
Royal Victoria Infirmary	0232 240503
Dublin	0001 379964
Birmingham	021 554 3801
Leeds	0532 430715
Newcastle	091 232 5131

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2 Craft AW. Circumstances surrounding deaths from accidental poisoning 1974–1980. *Arch Dis Child* 1983;**58**:544–6.
3 Craft AW, Lawson GR, Williams H, Sibert JR. Accidental childhood poisoning with household products. *BMJ* 1984;**288**:682.
4 Sibert JR, Clarke AJ, Mitchell MP. Improvements in child resistant containers. *Arch Dis Child* 1985;**60**:1155–7.
5 Taylor EA, Stanfield SA. Children who poison themselves. *Br J Psychiatry* 1984;**145**:127–35.
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9 Scherger DL, Wruk KM, Kulig KW, Rumack BH. Ethyl alcohol containing cologne, perfume and after shave. Ingestions in children. *Am J Dis Child* 1988;**142**:630–2.

Routine urines

Most children seen at a hospital either as an inpatient or an outpatient have a dipstick urine test and many have urine microscopy. In a report from Memphis, Tennessee, Mitchell and Stapleton (*Pediatrics* 1990;**86**:345–9) question whether routine urine testing is worthwhile. Urine analyses (dipstick and microscopy) were performed on 732 patients who had no clinical problem for which urine analysis would be regarded as necessary. An abnormality was found in 20% of urines: 12% had pyuria, 9% haematuria, 4·5% glycosuria, and 4% proteinuria.

Although routine urine testing was allegedly mandatory hospital policy, in practice it was done on only 30% of children and when an abnormality was found it was usually ignored (70% of abnormal results were not followed up). The only diagnoses made as a result of screening were of urinary infection in six patients. The authors conclude that routine urine analysis is costly and nonproductive. They have, however, shown that it gives a high yield of abnormal results but they have not been able to demonstrate the significance of those findings. Perhaps they should concentrate more on staff education than on test dismissal. If 70% of abnormal tests on my unit got ignored I don't think writing a paper about it would be the first thing to come to mind.

ARCHIVIST

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DEFINITIONS IN RESEARCH

Establishment of working definitions in nocturnal enuresis

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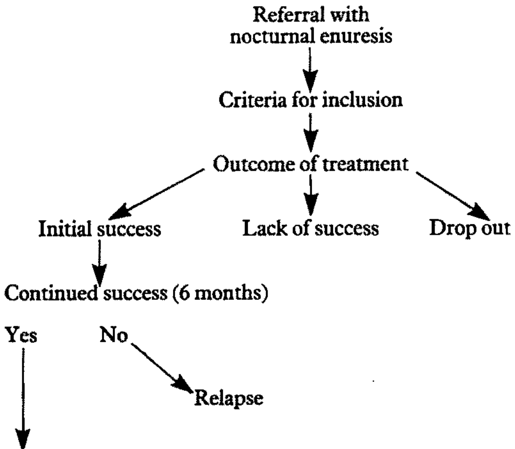
Studies of childhood nocturnal enuresis have traditionally used various criteria both to select children for treatment and measure its outcome. To make comparison possible among studies an agreed set of working definitions are needed.[1] The figure gives a flow chart by which the terms used in this paper are placed in context.

Inclusion criteria

The following characteristics of enuretics being studied should be included:

- Age, including the range for acceptance in the study, and the mean and actual age range of those children enrolled
- Number of boys and girls
- Presence or absence of organic disease
- Number of children with associated diurnal enuresis (such children may respond differently to treatment interventions).[2] 'Daytime wetting' requires definition and may be the occurrence of one or more daytime wetting incidents over a two week period
- The severity of bedwetting before treatment. In a review of 32 studies,[1] only 38% of papers reported severity: moreover the number of wet nights/week to be included in the study ranged from one to seven.[2 3] A baseline period of observation is recommended: from the patient's point of view four weeks is probably the maximum length. The suggested inclusion criterion for an individual child is 50% or more wet nights in a two week period.



A flow chart of nomenclature.

When the emphasis of a study is focused on those children who wet less than 50% of nights and are more difficult to treat, the degree of severity of wetting should be clearly stated.

Initial success

Initial success is usually described as the achievement of 'an extended number of dry nights'. A working definition requires consideration of two issues: an agreement on what constitutes 'an extended number of dry nights', and the necessity to specify the duration of treatment. I reviewed a range of published reports to clarify the criteria used in practice (table 1). Reports were included in the analysis if they fulfilled the following criteria:

- They were published since 1969 (covering the last 20 years)
- At least 12 children in the study received treatment
- A definition of 'initial success' was included in the methods section
- Treatment was of a 'conditioning' nature (that is, pad and bell, body alarm or dry bed training). These were chosen because of their established effectiveness.

Thirty five studies (90%) used the completion of a particular number of consecutive nights to define initial success and 27 (69%) selected 14 as that number. Thus 14 consecutive dry nights seems to be an acceptable consensus definition of initial success.

A specified duration of treatment was considered important, as protracted treatment is increasingly influenced by spontaneous remission and thus less confidence can be given to treatment as the effective variable. Two measures of duration of treatment have been used: firstly, a number of trials of the treatment. An arbitrary number of 50 buzzer soundings was selected and if children failed to achieve the initial success criteria during this time they were considered to have failed.[4 24] The limitation of such a measure lies in its specificity; it is only applicable to treatment with an enuresis alarm. Secondly, number of weeks of treatment. This is the most common method, and table 2 summarises the studies according to duration of

Table 1 Criteria for successful treatment of enuresis used in 42 studies

Study and method used	*Year of publication*	*Country of origin*	*Definition of initial success (No of consecutive dry nights)*	*Duration of treatment unless otherwise stated*
Pad and bell:				
Baker[4]	1969	USA	14	10
Berg *et al*[5]	1982	UK	On average <once a week in a four week period	16 (average)
Bollard and Nettelbeck[6]	1981	Australia	14	20
Butler *et al*[7]	1988	UK	14	16
Butler *et al*[8]	1989	UK	14	16
Collins[9]	1973	USA	10	8
Dische[10]	1971	UK	21	52
Dische *et al*[11]	1983	UK	21	No limit
Fielding[2]	1980	UK	14	12
Fielding[12]	1985	UK	14	14
Finley *et al*[13]	1982	USA	14	No limit
Fordham and Meadow[14]	1989	UK	42	16 (extended to six months)
Forsythe and Redmond[15]	1970	UK	28	30
Goel *et al*[16]	1984	UK	<Four in 28	20
Houts *et al*[17]	1986	USA	14	16
Jehu *et al*[18]	1977	UK	14	16
McConaghy[19]	1969	Australia	14	10
Netley *et al*[20]	1984	Canada	2 month	Not given
Sacks and DeLeon[21]	1978	USA	13	Not given
Taylor and Turner[22]	1975	UK	No more than one 'accident in 28 nights	Not given
Turner *et al*[23]	1970	UK	14	4
Wagner *et al*[24]	1982	USA	14	14
Wagner and Matthews[25]	1985	USA	14	12
Young and Morgan[26]	1972a	UK	14	Not given
Body alarm:				
Arroe and Barner-Rasmussen[27]	1979	Denmark	14	1–11 (months)
*Butler *et al*[8]	1989	UK	14	16
*Fordham and Meadow[14]	1989	UK	42	16 (extended to six months)
Moffat *et al*[28]	1987	Canada	14	Not given
Shapiro[29]	1985	USA	21	5–36 (months)
Dry bed training:				
Azrin *et al*[30]	1974	USA	14	Not given
Azrin *et al*[31]	1979	USA	14	Not given
Azrin and Thienes[32]	1978	USA	14	Not given
Besalel-Azrin *et al*[33]	1980	USA	14	6 (months)
*Bollard and Nettelbeck[6]	1981	Australia	14	20
Bollard and Nettelbeck[34]	1982	Australia	14	20
Bollard *et al*[35]	1982	Australia	14	8
Bollard and Woodroffe[36]	1977	Australia	14	Not given
Breit *et al*[37]	1984	USA	14	Not given
*Butler *et al*[7]	1988	UK	14	16
Doleys *et al*[38]	1977	USA	14	6
Griffiths *et al*[39]	1982	UK	14	22
Keating *et al*[40]	1983	USA	14	25

*Study design same as that in pad and bell study.

Table 2 Studies summarised according to number of weeks of treatment

No of weeks of treatment	*Pad and bell*	*Body alarm**	*Dry bed training**	*Total*
4–6	1	0	1	2
8	1	0	1	2
10	2	0	0	2
12	2	0	0	2
14	2	0	0	2
16	6	0	0	6
20	2	0	1	3
Other	2	2	3	7
Not given	7	1	5	13
Total	25	3	11	39

*The two studies comparing body worn alarm with pad and bell, and the two studies comparing dry bed training with pad and bell are included in the pad and bell column.

treatment. A third of the studies failed to specify duration of treatment. In the others a wide variety of treatment lengths (from four weeks to 36 months) were used, with 16 weeks as the most common.

An average course of treatment for the pad and bell is five to eight weeks.[41] Thus studies in which treatment lasts less than eight weeks exclude all but the fast responders, and consequently underestimate the success rate. As the average annual spontaneous cure rate between 5 and 9 years is 14%, however, and between 10 and 19 years is 16%, the longer the treatment the less confidence that can be attributed to the treatment itself. Duration of treatment might therefore be considered appropriate within a range of 12 to 20 weeks. As 16 has been used most frequently (nine studies from five different centres), this has been selected as the preferred option.

Thus a proposed definition of initial success is the achievement of 14 consecutive dry nights within a 16 weeks' treatment period. Conversely, lack of success would be accepted if treatment failed to meet these criteria.

'Drop outs'

A third possible outcome is premature stopping of treatment. This may occur for a number of reasons which have been classified as 'drop outs' for the reasons given below.

(i) Failure to attend. This generally means that after an initial appointment, a number of subsequent appointments are missed without notice or explanation.

Reasonable clinical practice suggests that failing to attend on two consecutive occasions can be considered as dropping out. Research protocols need to specify the degree and type of contact. There is an assumption that missed appointments mean that the patient 'has voted with his feet'. There are, however, many variables associated with missed appointments, and it may be that some children stop attending because bladder control has been achieved and appointments are considered unnecessary. For example, in one investigation 19% of the children stopped treatment prematurely because they had become dry.[44] A further reason for non-attendance is the practical difficulty of getting to clinic appointments. Research investigations should attempt to delineate whether drop outs through failure to attend are successes (either using the initial success criteria or parent imposed criteria) or failures.

(ii) The family wishes to discontinue treatment. For whatever reasons, if the child and parent wish to withdraw from treatment this is considered a drop out.

(iii) The doctor wishes to discontinue treatment. There may be instances where the doctor takes a clinical decision to stop treatment. This too constitutes a drop out.

(iv) The parents or the child may not accept treatment.[12] It might be argued that as treatment has yet to be initiated it cannot be viewed as 'premature stopping of treatment' and does not therefore constitute a drop out. Thus a proposed definition of drop out is that, after an initial appointment, two consecutive appointments are missed without notice, or treatment is discontinued by agreement by parent, child, or doctor. Protocols should endeavour to differentiate drop out successes from drop out failures.

Relapse

Relapse is generally accepted to mean a return to regular bedwetting after a period of being dry.[42] What, however, constitutes 'regular wetting'? Adoption of the stringent criterion that relapse was a single wet incident in the six months after a treatment success resulted in an 80% relapse rate.[45] This suggests that only a small number of children will remain completely free of bedwetting accidents once treated, a result that has been replicated in several studies.[9 46] It has been argued, however, that occasional bedwetting accidents after initial success should not be considered relapse on the grounds that (i) occasional bedwetting occurs among 'normal' or non-enuretic children, and (ii) bladder control may continue to be 'vulnerable' for some time and bedwetting may occur at times when the child is ill or under stress. Such lapses of control remit spontaneously and do not predict further relapse, suggesting that a definition of relapse should take this into account.[46]

Table 3 Definitions of relapse used in 24 studies

Study	*Definition of relapse*
Azrin *et al*[31–33]	More than three consecutive nights of bedwetting
Bollard *et al*[6 34–36]	One wet night/week over a 4 week period
Breit *et al*[37]	Two wet nights in any seven day period
Butler *et al*[7 8]	Two wet nights in any one week
Collins[9]	More than one wet in two weeks
Dische[10 11]	One or more wet night in four consecutive weeks
Fielding[2 12]	Two wet nights in any one week
Finley *et al*[13]	More than three wet nights/week for two weeks
Griffiths *et al*[39]	More than one wet night in a month
Houts *et al*[17]	At least one wet night in two consecutive weeks
Keating *et al*[40]	Three consecutive wet nights
Sacks and DeLeon[21]	One wet night/week for four weeks
Taylor and Turner[22]	More than one wet night/week at any stage
Turner *et al*[23]	At least one wet night/week in any two consecutive weeks
Wagner *et al*[24 25]	Three wet nights in any period of 14 nights
*Williams *et al*[47]	Three wet nights or more a month

*This is a follow up of the study by Doleys *et al.*[38]

The acceptance of occasional wet nights into a definition of relapse has, however, resulted in a wide variety of definitions (table 3). The 16 centres reported 10 different definitions. To examine these, a number of hypothetical cases were put forward. Table 4 shows to what extent relapse was accepted for six different cases using each definition. There was: (i) no unanimity for accepting relapse; (ii) a range of acceptance from more than three wet nights/week for two weeks—indicating no relapse—to more than one wet night/month, in which case relapse was judged to be universal; (iii) difficulty in applying some definitions because of ambiguity.

The most popular definitions were: more than one wet night/week (four centres), and one wet night/week over four weeks (three centres). The creation of an acceptable definition depends on agreeing about: the duration of monitoring, the elapsed time—that is, the length of time for which wet nights are observed—and the number of wet nights.

DURATION OF MONITORING

Nearly all relapses, however defined, occur within the first six months of treatment.[11 21 42 46] Thus regular monitoring of progress for six months after initial success seems to be good practice.[43] Relapse during this six month period usually indicates the need for retraining, whereas an absence of relapse might be considered to be continued success. As relapse is uncommon after six months, a two year period of monitoring has been advocated during which the follow up would be less intensive than during the first six months.[15] Complete success has been suggested to describe those children who do not relapse within two years of their initial success.[1 46]

ELAPSED TIME

The options considered could be number of weeks, number of days, or number of consecutive wet nights.

Table 4 Diagnosis of relapse for each definition for six hypothetical cases

Definition	*No of wet nights/week for four weeks*					
	Case 1 (*1, 1, 1, 1*)	*Case 2* (*1, 0, 6, 0,*)	*Case 3* (*0, 0, 2, 0*)	*Case 4* (*1, 3, 0, 0,*)	*Case 5* (*2, 2, 0, 2*)	*Case 6* (*1,1,2,0*)
More than one wet night/week[2 7 8 12 22 37]	No	Yes	Yes	Yes	Yes	Yes
One wet night/week over four weeks[6 10 11 21 34–36]	Yes	Uncertain	No	Uncertain	Uncertain	Uncertain
At least one wet night in two consecutive weeks[17 23]	Yes	Yes	No	Yes	Yes	Yes
More than three consecutive wet nights[31–33]	No	Uncertain	No	Uncertain	Uncertain	No
More than one wet night in two weeks[9]	Yes	Yes	Yes	Yes	Yes	Yes
More than three wet nights/week for two weeks[13]	No	No	No	No	No	No
More than one wet night/month[39]	Yes	Yes	Yes	Yes	Yes	Yes
Three consecutive wet nights[40]	No	Yes	No	Uncertain	Uncertain	Uncertain
Three wet nights in any 14[4 5]	No	Yes	No	Yes	Yes	Yes
Three wet nights or more/month[47]	Yes	Yes	No	Yes	Yes	Yes

Number of weeks

This is the most popular, the possibilities being one week (first definition), two weeks (third, fifth, and sixth definitions) or four weeks (second definition) (table 4). Two definitions (the seventh and tenth) give a month as the elapsed time but this suggests a less precise measure, because of the variable number of days in a month. Extending the time over which the definition applies introduces further complexity. For example, the second definition (one wet night/week over four weeks) might mean that a child who had one dry week but then wetted severely during the other three weeks would not be considered to have relapsed. This indicates that wet nights/week over a number of weeks should be avoided.

Number of days

Two examples are two wet nights in any seven day period,[38] and three wet nights in any 14.[25 26] Such definitions seem to emphasise the number of wet nights over a shifting period of time (any seven or 14 consecutive nights), which avoids the problem of number of wet nights/week over a specified period of time. This might provide a more clear cut criterion of relapse.

Number of consecutive wet nights (fourth and eighth definitions)

The merit of this option is that it avoids the need for an elapsed time. Using a number of consecutive nights, however, suggests that a child might be wetting four or five times a week and were these not on consecutive nights a relapse would not have been diagnosed.

The preferred options (without specifying the number of wet nights) might therefore be considered as: more than wet night/week (first definition); more than wet night in two weeks (fifth definition); or one wet night in any 14 (ninth definition).

THE NUMBER OF WET NIGHTS

The number of wet nights beyond which relapse is indicated must at this stage be a somewhat arbitrary choice. Taking the preferred options the maximum number of wet nights allowed before a relapse would be judged is: first definition—one wet night a week; fifth definition—one wet night over two weeks; or ninth definition—two wet nights in any 14.

It seems therefore that the first and ninth definitions are in agreement in allowing two wet nights over two weeks or 14 nights. The options then look like this: more than one wet night a week (first definition); more than two wet nights in two weeks; or more than two wet nights in any 14 (ninth definition).

The first option is the most commonly used, but the second and third are consistent with the initial definition of success in using 14 consecutive nights. All three options are sensitive in detecting relapse in the six hypothetical cases (table 4), and indeed options 2 and 3 give identical results.

Taking note of the lack of agreement between workers, the appropriate view might be to adopt option 2, a succinct yet easily applied definition that accepts the occurrence of occasional wet nights. Thus a proposed definition of relapse is more than two wet nights over two weeks.

Summary of definitions

SEVERITY

For inclusion in a research study a child should have 50% or more wet nights in two weeks.

INITIAL SUCCESS

The achievement of 14 consecutive dry nights within a 16 week treatment period. As a measure of the effectiveness of treatment the average number of weeks taken to reach the initial criteria of success might be a useful variable.

LACK OF SUCCESS

Failure to meet the initial criteria of success excluding drop outs.

DROP OUTS

After an initial appointment, two consecutive appointments are missed without notice, or treatment is discontinued by agreement by parents, child, or doctor. The clinician should endeavour to discover whether the drop out was a success or a failure.

RELAPSE

More than two wet nights in two weeks. The time between initial success and relapse should be stated.

CONTINUED SUCCESS

No relapse in the six months after initial success.

COMPLETE SUCCESS

No relapse in the two years after initial success.

I am grateful to the Enuresis Resource and Information Centre (Institute of Child Health, Bristol) for their support and to Professor David Baum, Penny Dobson, Steven Hunt, Professor Roy Meadow, Roger Morgan, Mary McGraw, John Osborne, Paul Stallard, Betty Tribe, and Heather Williamson (all of whom are members of the National Enuresis Research Steering Group) for their comments on early drafts of this paper. I am also indebted to Amanda Pullan for typing the manuscript.

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LETTERS TO THE EDITOR

Circulatory effects of fast ventilator rates in preterm infants

SIR,—Fenton *et al* have recently described the circulatory effects of fast ventilator rates in critically ill neonates.[1] These authors found a decrease in arterial oxygen tension (PaO_2) with an increase in ventilator rate and have concluded that this fall in PaO_2 was a result of the predicted theoretical fall in mean airway pressure with increasing rate.

Mean airway pressure can be calculated from the following formula:

$$\frac{(IT\times PIP)+(ET\times PEEP)}{IT+ET}$$

(where IT=inspiratory time, ET=expiratory time, PIP=peak inspiratory pressure, and PEEP=positive end expiratory pressure). It can also be directly measured through a transducer and should essentially reflect the area under the ventilator pressure curve. As can be seen from the above formula, if the inspiratory:expiratory ratios are kept constant and there is no significant change in peak inspiratory pressure or PEEP, then mean airway pressure should remain constant as rate is changed. A critical determinant of whether mean airway pressure will in fact change under these circumstances will be the shape of the ventilator pressure curve, which will be affected by the lung compliance and the gas flow to the ventilator.

We have tested this hypothesis by subjecting an Infant Star (Infrasonics) and a Sechrist Model IV-100B (Sechrist Industries) to the changes that were made by Fenton *et al* for rates of 30 (IT=ET=1), 60 (IT=ET=0·5), and 100 breaths/mintue (bpm) (IT=ET=0·3) with a constant inspiratory (20 cm H_2O) and expiratory pressure (5 cm H_2O).

We measured mean airway pressures using an independent transducer and both ventilators were connected to a test lung with a compliance of 1 ml/cm H_2O. There was no change in mean airway pressure for the Infant Star with the ventilator flow varied between 8 and 18 l/minute. For the Sechrist, the same model used by Fenton *et al*, the mean airway pressure at 30 and 60 was 12 cm H_2O and at 100 bpm was 11 cm H_2O at a flow of 10 l/minute. If the flow at 100 bpm was increased to 15 l/minute, then the mean airway pressure was also 12 cm H_2O. Our results also confirm the observations of Greenough and Greenall.[2]

We believe that the fall in oxygenation associated with the higher ventilatory rates may reflect an inadequate period of time above the opening pressure of the terminal airways in infants with significant respiratory disease, as opposed to any significant change in mean airway pressure.

We believe that the fall in oxygen tensions observed in the current study reflect mechanisms other than those suggested by the authors.

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1 Fenton AC, Field DJ, Woods KL, Evans DH, Levene MI. Circulatory effects of fast ventilator rates in preterm infants. *Arch Dis Child* 1990;65:662–6.
2 Greenough A, Greenall F. Performance of respirators at fast rates commonly used in neonatal intensive care units. *Pediatr Pulmonal* 1987;3:357–61.

SIR,—We read with interest the recent paper by Dr Fenton and colleagues but feel that certain points require comment.[1] Firstly, it is not necessary to postulate an effect on shunting to explain the rise in arterial oxygen tension when the biased flow was turned off. The more likely mechanism is via an effect on mean airway pressure. Turning on the bias flow could shorten the positive pressure plateau reducing mean airway pressure. We should be most interested to see data on mean airway pressures generated in the study.[1]

Secondly, the observations on tidal volume are surprising. Field *et al* previously reported that tidal volume is maintained until inspiratory time is reduced below 0·3 seconds,[2] yet in this present study[1] at 60 breaths/minute (bpm) there is already a 25% reduction in tidal volume.[1] This suggests very short inspiratory times were used; this information is not given.[1]

Thirdly, unfortunately, the paper of Greenough *et al* is misquoted.[3] In that paper changes in positive end expiratory pressure (PEEP) were documented as not occurring with the Sechrist ventilator at rates up to 120 bpm, as this ventilator incorporates an assisted expiratory valve, which prevents inadvertent PEEP at flow rates even up to 20 l/minute.[3,4] Increasing the flow rate at high rates restores the shape of the waveform, maintaining mean airway pressure without altering the PEEP.[3] In that study of Greenough *et al* the inspiratory:expiratory (I:E) ratio was held constant at 1:1·2. It has been subsequently shown that with such an I:E ratio, inadvertant alveolar PEEP occurs in paralysed infants at rates of 100 bpm,[5] preventing a fall in carbon dioxide at the fastest ventilation rate.[3] It is likely that the difference in the results of the earlier study[3] and Fenton *et al*[1] could be the use of different I:E ratios. Again, data on the I:E ratios used would be helpful.

Fourthly, the results of Fenton *et al* are given only as mean and standard errors, it is thus not possible to determine if all the babies studied generated the same pattern. This seems unlikely as the patients were of very varied postnatal ages (range 14–216 hours) and birth weights (720–2420 g) and of different ventilatory requirements (fractional inspiratory oxygen 0·35–1·0; peak inflation pressure 15–35 cm H_2O). In particular, it would be more informative to have the results of individual babies' tidal volumes expressed as ml/kg.

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Antiviral and antibacterial lipids in human milk and infant formula

SIR,—We read with great interest the recent article by Isaacs *et al* in which they conclude that the antiviral and antibacterial activities of lipid extracts from gastric aspirates in infants probably result from intragastric lipolysis by lingual lipase to monoglycerides and fatty acids from the triglycerides of the original feeds.[1] Lingual lipase hydrolyses medium and short chain triglycerides at a higher rate than longer chain fats.[2] In the study by Isaacs *et al*, at least 50% of the fat content of both formulas was medium chain triglyceride if the additional coconut oil is taken into account. Hydrolysis of milk fat by lingual lipase produces a large amount of monolauryl glycerol, which has been shown to have appreciable antibacterial, antiviral, and antifungal activities.[3]

We have recently shown a similar effect in mice, where by modifying the mother's dietary fat intake we were able to change the fatty acid composition of their milk. The offspring were inoculated orally with EDIM rotavirus. In those young mice fed on milk naturally enriched with lauric acid (C12) and other medium chain fatty acids, the onset of diarrhoea was delayed and the stool excretion of rotavirus was appreciably reduced by comparison with mice fed on milk of different fatty acid composition (unpublished observations).

At least in mice, therefore, and contrary to the assertion of Isaacs *et al*, the protective effects of milk fatty acids appear to operate against non-enveloped viruses as well as enveloped viruses and bacteria. We cannot, of course, rule out the possibility that other mechanisms such as secondary variation in trypsin secretion could be responsible for our observations,[4,5] but we think that this is inherently unlikely.

It is becoming increasingly clear that milk fat, whether human or of animal origin, has important protective value against intestinal infection. Skimmed milk should not be used as a food source for young children unless there is a strong medical reason for the withholding of fat, and this policy should be followed particularly in countries with a high incidence and severity of gastroenteritis.

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1 Isaacs CE, Kashyap S, Heird WC, Thormar H. Antiviral and antibacterial lipids in human milk and infant formula feeds. *Arch Dis Child* 1990;65:861–4.
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Dr Isaacs comments:
I certainly agree with Professor Dodge and Dr Sagher that milk lipids may provide important protective effects. Further, I find their observation that alterations in the medium chain fatty acid composition of mouse milk may reduce the severity of infection from rotavirus, a non-enveloped virus, extremely interesting. We, of course, did not determine the effect of the stomach contents of infants fed the various formulas on non-enveloped viruses. Rather, our statement that milk fatty acids and monoglycerides have antiviral activity against enveloped viruses but not non-enveloped viruses was based upon the results of a number of studies by us and others showing that only enveloped viruses are inactivated by milk lipids or purified lipids.

In the early studies of Welsh *et al* enveloped Semliki Forest virus and herpes simplex virus type 1 (HSV-1) were inactivated by milk lipids but enterovirus coxsackie B4, a non-enveloped virus, was not.[1] In addition, we found that human milk inactivated the enveloped measles virus, vesicular stomatitis virus and HSV-1 but not the non-enveloped vaccinia virus and poliovirus.[2] Milk lipids also have been shown to inactivate dengue virus[3] and mouse mammary tumour virus[4]; these are both enveloped viruses.

In in vitro studies it has been found that purified free fatty acids and their derivatives inactivated the enveloped Sendai virus, Newcastle disease virus, influenza A virus, Sindbis virus, West Nile virus, HSV-1, and a number of enveloped bacteriophages but not the non-enveloped SV40, polio or encephalomyocarditis viruses (ECMV).[5 6] This antiviral effect appeared to be due to the destruction of viral envelopes.[7]

These multiple findings suggest that the apparent protective effect of milk lipids against rotavirus infection observed by Dodge and Sagher is unlikely to be due to direct inactivation of the non-enveloped rotavirus. However, milk fatty acids may prevent the binding of rotavirus and other non-enveloped viruses to receptors or interfere with viral uncoating. These suggestions are supported by the observations of JFE Newman (Institute for Virology, Sandringham, South Africa), reported at the recent VIIIth International Congress of Virology (Berlin, 1990), that fatty acids with chain lengths of 12–15 prevent uncoating of some non-enveloped viruses, for example, bovine enterovirus and ECMV, but not others, for example, poliovirus type 1, coxsackie B5, and human rhinoviruses 1B and 14. It would, therefore, be interesting to see the results of an in vitro study examining the effects of medium chain fatty acids found in mouse milk on rotavirus infectivity.

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Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis

SIR,—I read with interest the paper by Drs Dalzell and Heaf,[1] particularly as we had a very similar study published in the *Archives* four years previously (to which no reference was made!).[2] In both studies the index cases and controls were similar in age and number, but we prescribed double the dose of fluorescein dilaurate than did Dalzell and Heaf. Our study also demonstrated significantly different fluorescein dilaurate excretion ratios between patients with cystic fibrosis and normal subjects, with the ratios being significantly reduced in patients with cystic fibrosis ($p<0{\cdot}01$). An additional component to our study was to compare the fluorescein dilaurate test with faecal chymotrypsin estimation. We found a positive correlation between the two tests ($R=0{\cdot}69$, $p<0{\cdot}02$).

Although the fluorescein dilaurate test appears to detect exocrine pancreatic insufficiency, in practice it is of limited value as it is in capsule form and not suitable for the age group in which the presentation of cystic fibrosis is most prevalent. We did explore the possibility of the test being used to titrate pancreatic supplement administration. If cholesterol ester hydrolase, which is responsible for liberating the fluorescein from fluorescein dilaurate, was incorporated into a pancreatic enzyme supplement, it may be possible to use the fluorescein dilaurate test to determine the most effective dosage of pancreatic enzyme for individual patients. Unfortunately this enzyme does not appear to be present in any of the commercially available preparations.

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1 Dalzell AM, Heaf DP. Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis. *Arch Dis Child* 1990;**65**:788–9.
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Hospital admission—a missed opportunity to immunise

SIR,—We agree with the conclusion of Ferson's study that there is poor documentation of a child's immunisation status on admission to hospital.[1] In 66% of the children admitted to our hospital and verified to have incomplete immunisation the 'medical record of immunisation' was absent or in so shortened a form as to be meaningless.

Using information from the district computer we determined the immunisation status of children from Salford district who were admitted to a general paediatric ward in a teaching hospital during November 1989. We also obtained details about the children verified to have incomplete immunisation, including the recorded immunisation history, from the hospital notes.

There were 139 admissions of 133 Salford children during the month. The children's ages ranged from 7 days to 15 years with 113 under 5 years of age. Using the immunisation schedules recommended at that time, information from the district computer showed that 70 children were fully immunised and 47 incompletely immunised; 16 were not traced by the computer.

Information from the hospital notes suggested that in five children there was a contraindication to immunisation and three children had received the necessary immunisation within the two weeks before admission. The hospital notes for six children were not available. The remaining 33 children could have been offered: triple antigen ($n=14$), oral polio ($n=14$), combined diphtheria-tetanus ($n=1$), measles-mumps-rubella ($n=22$), tetanus ($n=3$), and pertussis immunisations ($n=12$).

Using Ferson's classification of the 'medical record of immunisation' in the hospital notes,[1] in 27 of the 41 notes (66%) documentation was absent or unclear. In two (5%) it was clear but incorrect, and documentation was correct and clear in only 12 (29%) of notes.

At our children's hospital, sited in a district with poor immunisation uptake, the opportunities for immunisation in a single month on one ward are considerable. To immunise in hospital we need accurate information on previous immunisations. Parental recall and medical recording of immunisation provide inadequate data. Two possible solutions are improving access to immunisation information held on district computers and using parent held child health records.

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Effects of overweight on lung function

SIR,—We were very interested in the paper by Dr Fung and colleagues on overweight and lung function,[1] but we have some queries about their approach and conclusion.

To investigate the association between body mass index and lung function in children, the authors included subjects up to 20 years of age. In table 1 they show that distribution of height for the sexes was unequal: 45% of all girls were taller than 150 cm but only 12% were taller than 159 cm. This suggests that most of these females had reached their adult height: at age 13, when 75% of Hong Kong girls reach menarche, the median height is 151 cm.[2] On the other hand, 31% of all boys were taller than 159 cm with no skewed distribution, suggesting that most boys had not reached adult height yet.

Hence, distributions of height and (maturational) age for gender differ considerably and adjustments by linear regression cannot alter this: comparisons remain difficult. Secular trends further complicate such analyses.[2,3] Because the height-lung function relationship during puberty is complex and varies with age and gender,[4,5] it is desirable to study the sexes before and after attaining adult height.

A contribution of body mass index to lung function may biologically relate to trunk size rather than fat distribution. Schwartz *et al* found correlations between body mass index and sitting height and concluded that sex related differences in lung function are partly explicable by the growth of the trunk.[6] Indeed chest circumference and biacromial width correlate—independently of stature—with body mass index (r=0·80 and 0·55, in 995 girls, R Veeneklaas, personal communication).

Explained variance is improved by body mass index but it is unclear if this holds equally for the whole age range studied, and it seems premature to infer that body mass has a positive effect on lung function in girls and in normal weight boys.

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Circulating malignant cells in Burkitt's lymphoma: possible role in tumour dissemination

SIR,—The tumour, Burkitt's lymphoma, arises as a clonal proliferation. In any individual patient the surface membrane immunoglobulin of the malignant cells has identical heavy and light chains.[1] It is usual at presentation for such patients to have multiple organ involvement. Necropsy studies have demonstrated multiple organ involvement in both African and non-African series.[2,3] Previous explanations for the widespread metastases have been principally that the tumour cells spread through anatomical channels and tissue layers, but it was not easy to explain metastases to the breast and thyroid via such routes.[3]

Circulating malignant cells can be identified in 25–50% of patients with Burkitt's lymphoma who have bone marrow involvement.[2] By examining at least three buffy coat smears stained routinely with Leishman's dye[4] we were able to detect malignant cells in the peripheral blood of 19 out of 25 patients in our centre who did not have bone marrow involvement. It is essential to obtain samples before chemotherapy because of the tumour's response to cytotoxic agents. We believe that multiple organ involvement in Burkitt's lymphoma results from deposition of circulating malignant cells within tissues. Such haematogenous spread can account for tumour masses in apparently aberrant sites.

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An emotional trigger mechanism for sudden infant death

SIR,—In their study of recurrent cyanotic episodes Southall *et al* suggest that the most common trigger was a sudden, naturally occurring stimulus from fear, anger, or pain.[1] Elements of 'surprise' and 'unexpectedness' were stressed. Cyanotic episodes were more common 'when there was a high level of emotional tension in the home, or when the routine of the child was interrupted'.

These observations lend strong support to the 'fear paralysis' hypothesis proposed in 1986 as a trigger mechanism for SIDS,[2,3] adding emotional/psychical factors to the list of theories attempting to explain the cause of suddent infant death syndrome (SIDS). This innate, atavistic reflex, present throughout the entire animal kingdom, precipitates cardiovascular and respiratory changes, which in animals may lead to death. The *stimulus* for the fear paralysis reflex is any threat perceived as a danger and which evokes fear, such as predator confrontation, restraint of movement (preventing flight), unfamiliar and sudden noises. The reflex is strengthened in a strange environment, in separation from the mother and companions, and in situations with which the organism is unable to cope. Elements of surprise, unexpectedness, and novelty were similarly emphasised.

On the *response* side, characteristic features of the fear paralysis reflex are an immediate motor 'paralysis' which includes generalised and prolonged immobility, reduced muscular tone, bradycardia, and unresponsiveness to external stimulation. The response pattern further includes strong and prolonged (20–30 second) arrest of respiration in expiration, and rises in systemic and pulmonary arterial pressure—that is, the same changes that are held responsible for the hypoxaemia in cyanotic episodes and SIDS in susceptible infants. Emotional responses as well as apnoeic episodes may show both primary increases and decreases in heart rate.

A further similarity between the fear paralysis reflex and the cyanotic episodes refers to their response to pharmacological agents. In animal experiments, fear paralysis was suppressed by clonidine and other anxiolytic drugs,[2] and these were proposed as a preventive means in infants at high risk for SIDS.[2] Southall *et al* have now demonstrated that such treatment with clonidine and tetrabenazine is effective.

In support of the fear paralysis reflex as an extrinsic trigger mechanism for SIDS is the observation that restraint of movement was considered a contributing factor to death in as many as every third case of SIDS.[4] Further, the excess of SIDS during weekends and holidays can only be explained by the operation of environmental trigger mechanisms.[5] Finally, Wennergren *et al* observed marked disturbance of the infant's daily rhythm and/or sleeping rhythm before death or the apnoeic episode in about 40% of the cases.[6]

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BOOK REVIEWS

Yearbook of Pediatrics 1990. Edited by FA Oski, JA Stockman III. (Pp 527; price not stated, hardback.) Yearbook Medical Publishers, 1990. ISBN 0-8151-6585-4.

This is the eleventh time that Professors Oski and Stockman have collaborated in the editing of the yearbook. Neither shows any sign of flagging and the commentaries are as lively and as entertaining as ever. The format is similar to previous editions except for the deletion of the synopsis of review articles. Key publications have been abstracted from a wide range of journals of English speaking nationalities.

In his foreword Professor Oski describes, with examples, the scope of the contents, how society and its problems touch on paediatrics (AIDS, maternal drug abuse, war, contraception), new diseases (human parvovirus and pestivirus infections), new therapies (heart-lung transplanatation for cystic fibrosis, laser treatment for naevi) and new signs (the closed eye sign in abdominal pain, the perineal eruption in Kawasaki disease). For general paediatricians the greatest value must surely be the discussion about controversial topics. The current treatments for bacterial meningitis are debated and referenced, the management of pyloric stenosis in the UK is provocatively criticised but not referenced, and the need to develop research techniques to discover the harm of recurrent otitis media is considered.

Many abstracts reflect practice and cultural issues in the United States. Tennis elbow in breast feeding mothers due to overzealous use of the breast pump, the perceived attractiveness of preterm infants with cranial moulding, the value of aerobic excercise in delinquent adolescents, may all strike readers in other countries as peculiarly American issues.

The commentaries are filled with observations and commonsense advice which reflect broad experience and extensive knowledge. Both editors write as they think. Time which might have been spent on improving the syntax is devoted to amplifying each abstract with further references on the topic. The anecdotes and schoolboy humour are both refreshing and informative. I was interested to learn, for example, that Dr Wizwell has become a successful urologist, and to discover the odd man out among herpes, AIDS, a condominium in Buffalo, and gonorrhoea (the last because it is the only one you can get rid of!).

It has been a pleasure to review and to recommend the yearbook.

S McKENZIE
Consultant paediatrician

Bone Marrow Transplantation in Children. Edited by F Leonard Johnson and C Pochedly. (Pp 551; $150 hardback.) Raven Press, 1990. ISBN 0-88167-575-X.

This is a well presented and conveniently sized book intended for 'paediatricians with interests in immunology, haematology, and oncology'. The style is clear and readable, with informative tables and illustrations, and quality printing and paper. In 28 chapters and 500 pages, the scope and contemporary practices of paediatric bone marrow transplantation are reviewed by numerous contributors, all from transplant centres in the United States. There is a thorough explanation of the underlying theory and principle of transplantation, guidelines on supportive care, and, of particular importance in paediatric practice, discussion of long term effects on growth and development. Nine chapters review the world experience of bone marrow transplantation for specific diseases, and in each case there are comments on individual preference and practice within the contributors' own unit. Although this approach leads to some repetition, this is not unduly tiresome. On occasion, recommended practice is contentious, but the reader is encouraged in the introduction to be critical in drawing conclusions.

I have two criticisms of this book. Firstly, as may be the case with any text, the literature of this subject has expanded rapidly resulting in gaps in some of the reviews. Secondly, there is little new information here for the experienced subspecialist. However, this is an informative and well referenced text which will be of considerable interest to all junior staff working in paediatric bone marrow transplantation and so is recommended for the departmental library.

DAVID WEBB
Lecturer in haematology

Paediatric Endocrinology. 2nd Ed. Edited by Fima Lifshitz. (Pp 1104; $234 hardback.) Marcel Dekker, 1990. ISBN 0–8247–8159–7.

This 2nd edition of *Paediatric Endocrinology* in the 'clinical paediatrics' series acknowledges the many recent advances in this field that have necessitated an updated, greatly expanded new version. In the foreword the reader is reminded that 35 years ago paediatric endocrinology in the USA was practiced by only 15 paediatric endocrinologists from two training centres as opposed to over 500 certified paediatric endocrinologists from multiple training centres at present. In addition, the broad base of endocrinology is noted with skills in genetics, nutrition, gynaecology, and auxology being needed in addition to those in paediatric endocrine disease.

The book is divided into six parts dealing with aspects of childhood endocrine disease covering growth and growth disorders, adrenal and sexual development, thyroid disorders, problems related to calcium and phosphorus, diabetes mellitus and hypoglycaemia, and other endocrine disorders. The latter section contains seven chapters covering areas such as autoimmune endocrinopathies, neuroendocrine disorders, childhood obesity, and low renin hypertension in childhood.

There is a chapter on tolerance testing in children which provides extensive details of various endocrine procedures. Several of the protocols noted are for tests that are not used frequently and should provide a useful reference source. The final chapter on reference charts is also extensive but many of them are based on American standards. However, there are useful reference charts for penile length, nipple size in various stages of puberty, and a useful selection of disease specific charts for conditions such as Down's syndrome, Prader-Willi syndrome, achondroplasia, and other skeletal dysplasias.

Having used this book as my main paediatric endocrine reference source for several weeks, I am impressed by the breadth of the information provided on several common areas. This is well illustrated by the section on growth and growth disorders. The initial chapter on short stature gives a comprehensive review that would be valuable to the non-specialist paediatrician and indicates the need for subsequent investigations. This contrasts with three chapters in this section on hereditary growth hormone deficiency, disorders of growth hormone, neurosecretion, and growth hormone treatment, which are very thorough reviews of topics of great interest to the specialist paediatrician in growth disorders.

The remaining chapters in this section covering areas such as psychosocial short stature, intrauterine growth retardation, failure to thrive, and excessive growth syndromes would be of interest to both specialist and non-specialist practitioners. The chapter on the psychological issues of short stature covers a subject that is rarely addressed in paediatric endocrine textbooks and provides a comprehensive review of the topic. It is also a reminder that the scientific appraisal and treatment of short stature has perhaps outstripped and overshadowed the immense psychological problems that can occur with restricted height.

The main sections of the book cover their subjects in both a wide ranging and detailed manner making it difficult to comment on these in a short review. The calcium and phosphorus section, however, is very worthy of special mention with an excellent review on calcium/phosphate homoeostasis followed by a detailed account of calcium and phosphorus problems in the neonate. It also covers parathyroid disorders in children and there is an excellent section on metabolic bone disease in children which is an area that one is often seeking an up to date reference source. There are 150 pages approximately devoted to diabetes mellitus in the child and these pages cover the subject extensively with the main chapters on management being from the Pittsburgh team led by Dr Allan Drash, with full discussions on complications, nutrition, treatment of diabetic ketoacidosis, diabetes education, together with the psychosocial aspects of this condition.

This book can be recommended for specialist practitioners in paediatric endocrinology as it provides a modern and wide ranging review of the speciality with extensive references. The introductory and physiological chapters in each section should appeal to the general paediatrician who might feel rather intimidated by the more specialised chapters in each section. There are few large textbooks of paediatric endocrinology but this one could be highly recommended, although its price will probably make it more likely to be found in the paediatric library rather than on the practitioners own book shelf.

C S SMITH
Senior lecturer in child health

Pediatric Otolaryngology. Vols 1 and 2, 2nd Edition. Edited by Charles D Bluestone, Sylvan E Stool, Mary D Scheetz. (Pp 1458; £180·00 each volume hardback.) W M Saunders Company (Harcourt Brace Jovanovich) 1990. ISBN (set) 0-7216-2120-1.

This is a second edition of a magnum opus on ear, nose, and throat diseases and allied subjects in children. It is a fairly massive two volume, seven section, 1458 page work, almost entirely from North America. Of the 119 contributors only six are Canadian and one is Japanese. The remainder represent individuals with a wealth of otolaryngological and paediatric experience from almost every centre of excellence in the United States. Interestingly, it is said to be aimed at all levels of medical staff from students, through house staff, paediatricians, and otolaryngologists, and there is certainly something for everyone in this edition. There is a bias in relation to otological disease, said by the authors to represent the most commonly occurring conditions treated by those who care for children. In many ways the otological emphasis also reflects the long term and wide ranging interest in ear diseases in children, originating in the Pittsburgh department where the authors are based. Few centres have contributed so much to the literature in relation to children's ear disease as have Professors Bluestone and Paradise. There are new and interesting chapters on the very topical subjects of sleep apnoea and snoring and also on subglottic stenosis and perilymphatic fistulae.

Generally speaking, each chapter is very well referenced and there are special selected references relating to key papers which are annotated. This provides the reader with a means to explore more fully the surgical management of conditions that are discussed in the text but which are not described in detail and are felt to lie outside the scope of the book. Most of the text is supported by clear, distinctive, and helpful line diagrams and the medical artist deserves acknowledgment for this.

The text is arranged in a problem orientated way and combined with an authoritative and comprehensive review of each subject. There are 100 page sections on craniofacial growth and on the neck and communication disorders. There are sections of 200 pages each on the nose and sinuses; on the face, orbit, mouth, pharynx and oesophagus; and finally on the larynx, trachea, bronchus, and oesophagus. More than 500 pages are devoted to ear and related structures. Within this section is a very comprehensive review of congenital anomalies of the ear.

There is absolutely no doubt that every ear, nose, and throat department must have this edition within their medical library. It is an essential reference book and, as claimed by the authors, it will provide points of interest and a means of stimulating the reader towards appropriate references for all aspects of ear, nose, and throat disease in childhood. Despite my enthusiasm for this book I was left wondering why not a single contributor was gleaned from the United Kingdom, Scandinavia, Australasia, or other centres where undoubtedly important contributions could have been found.

A RICHARD MAW
Consultant ear, nose, and throat surgeon

Graft-vs-Host Disease—Immunology, Pathophysiology and Treatment. Edited by SJ Burakoff, HJ Deeg, J Ferrara, K Atkinson. (Pp 816; $210 hardback.) Marcel Dekker, 1990. ISBN 0–8247–8188–0.

This book is destined to be a standard reference on the topic of graft versus host disease (GVHD) for the 1990s. The editors have drawn together from America, Europe, and Australia many of the foremost experts on GVHD to produce an attractive, well indexed, up to date book. At $210 it is expensive but good value for those working in bone marrow transplant units. As the number of paediatric disorders amenable to treatment with bone marrow transplant slowly increases, many paediatricians have become familiar with the chronic GVHD which sometimes ensues. For most paediatric department libraries this book would be an extravagance, but it would be worth a trip to the main library to consult if a question on the detailed management of GVHD arose.

The book is divided into two sections, each preceded by an introduction of eight pages which succinctly reviews the contents of each chapter. The first section of 300 pages, divided into 15 chapters, comprehensively reviews the animal experimental models which have perhaps proved more relevant to clinical transplantation than any other area of human disease. The next 400 pages deal with clinical aspects of GVHD in 24 chapters, providing a mine of information.

Is there nothing wrong with this book? Perhaps a lack of perspective, both in terms of the lack of an overview—the brief foreward by this year's Nobel laureate for medicine might have been expanded to do this—and also from a paediatric viewpoint. The incidence and severity of GVHD is inversely correlated with age but its treatment with immunosuppressants has particular implications for children, especially in terms of growth. These aspects are well covered in separate chapters but a chapter bringing these and other aspects of GVHD related to childhood would have complemented this book nicely.

GARETH MORGAN
Senior lecturer and consultant immunologist

Problem-oriented Pediatric Diagnosis. RM Barkin. (Pp 200; £9:95 paperback.) Churchill Livingstone, 1990. ISBN 0-316-08104-3.

I approached this book with mixed feelings. Is there a place for yet another pocket handbook of paediatrics? On the other hand, the title suggested that this book might occupy an unfilled niche in paediatric libraries.

The book is mainly grouped into problems according to systems, but there are also sections on the approach to the healthy child, general problems, and behavioural problems. The book seems to be aimed much more towards acute problems rather than chronic outpatient disorders. Thus abdominal pain is considered largely under surgical diagnoses with little mention of chronic abdominal pain. Furthermore, in this, as in most of the sections there is no indication of the relative importance of conditions in a differential diagnosis.

There were a number of minor irritations in this book. Some of the diagrams, such as the one on the evaluation of anaemia, would be well beyond the visual acuity of anybody with incipient presbyopia. I also found some of the American terms rather obtrusive, for example, stooling for defaecation.

Some of the recommended investigations reveal a definite difference in practice on the other side of the Atlantic, for example, recommending obtaining a catheter specimen of urine before suprapubic aspiration in infants with a suspected urinary tract infection. I was also surprised that electroencephalography was advised for all children presenting with seizures. Equally odd was the omission of the measurement of peak flow in the assessment of asthma. I doubt if many British paediatricians would advocate parents administering ipecacuanha unsupervised to their children at home, and yet this advice is given under the parental instruction guide.

Overall I found this an unhelpful book. There are many other pocket handbooks of paediatrics that I would recommend rather than this book. Despite the criticisms I gleaned at least one new fact from this book—that the black widow spider is a cause of abdominal pain, but, alas, the pathogenesis of this was not explained in the text!

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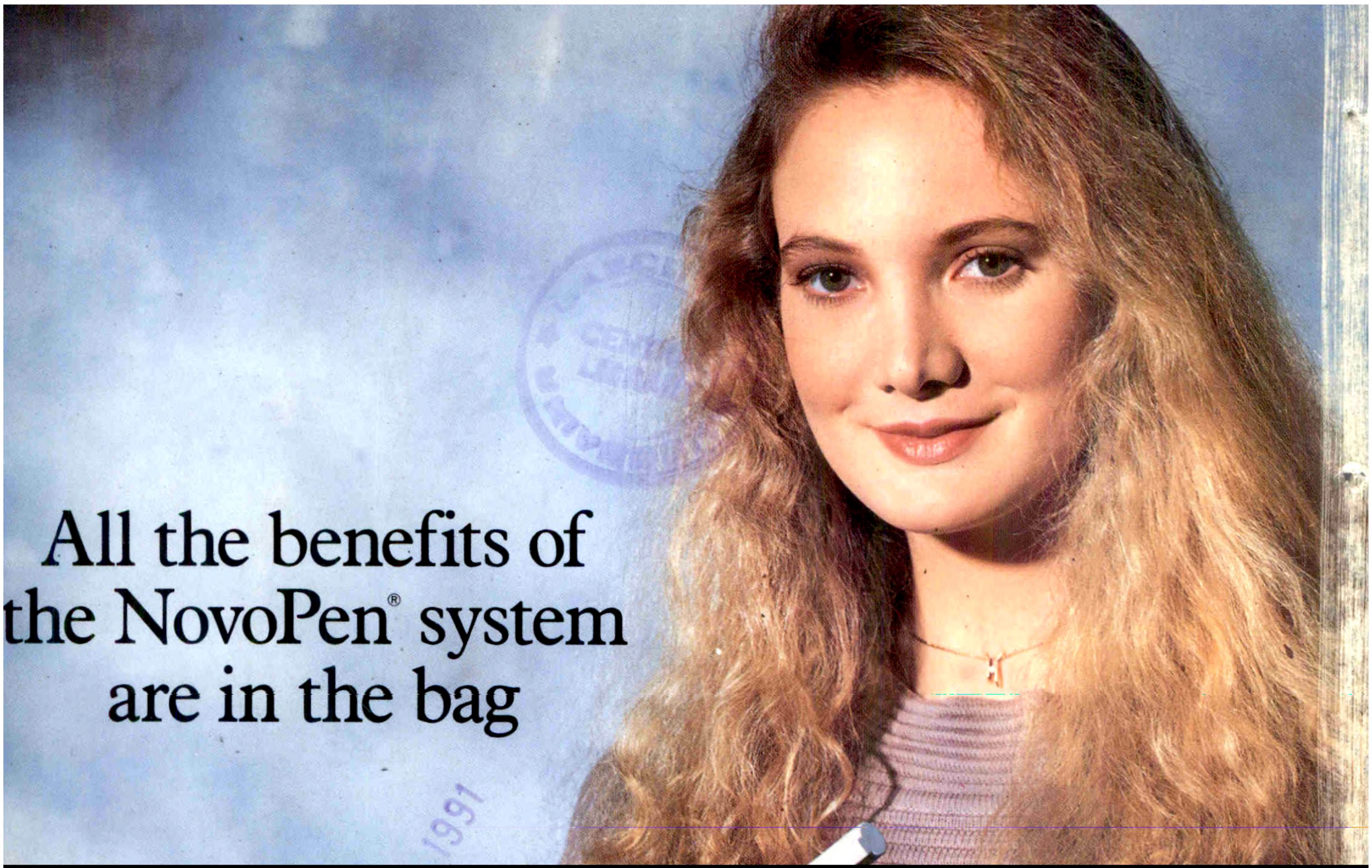

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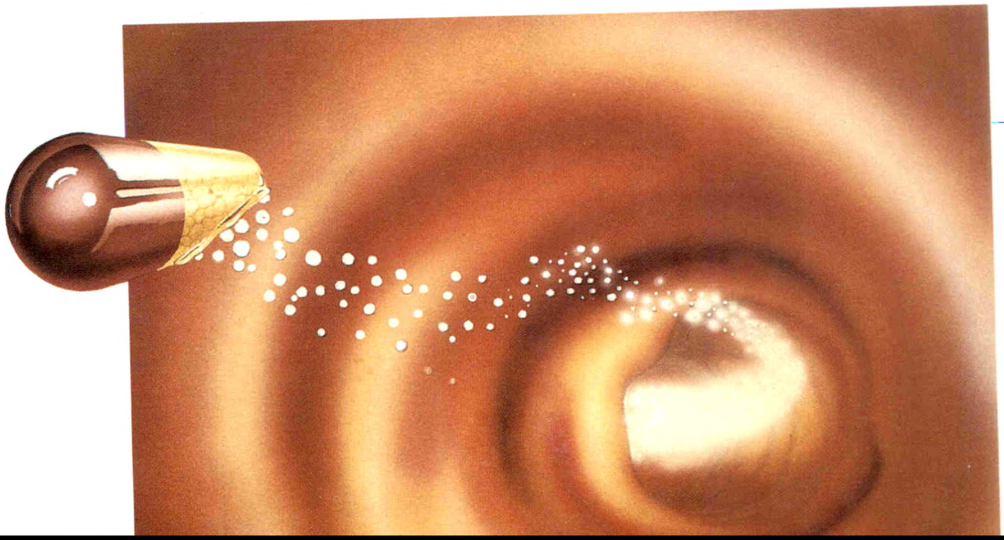

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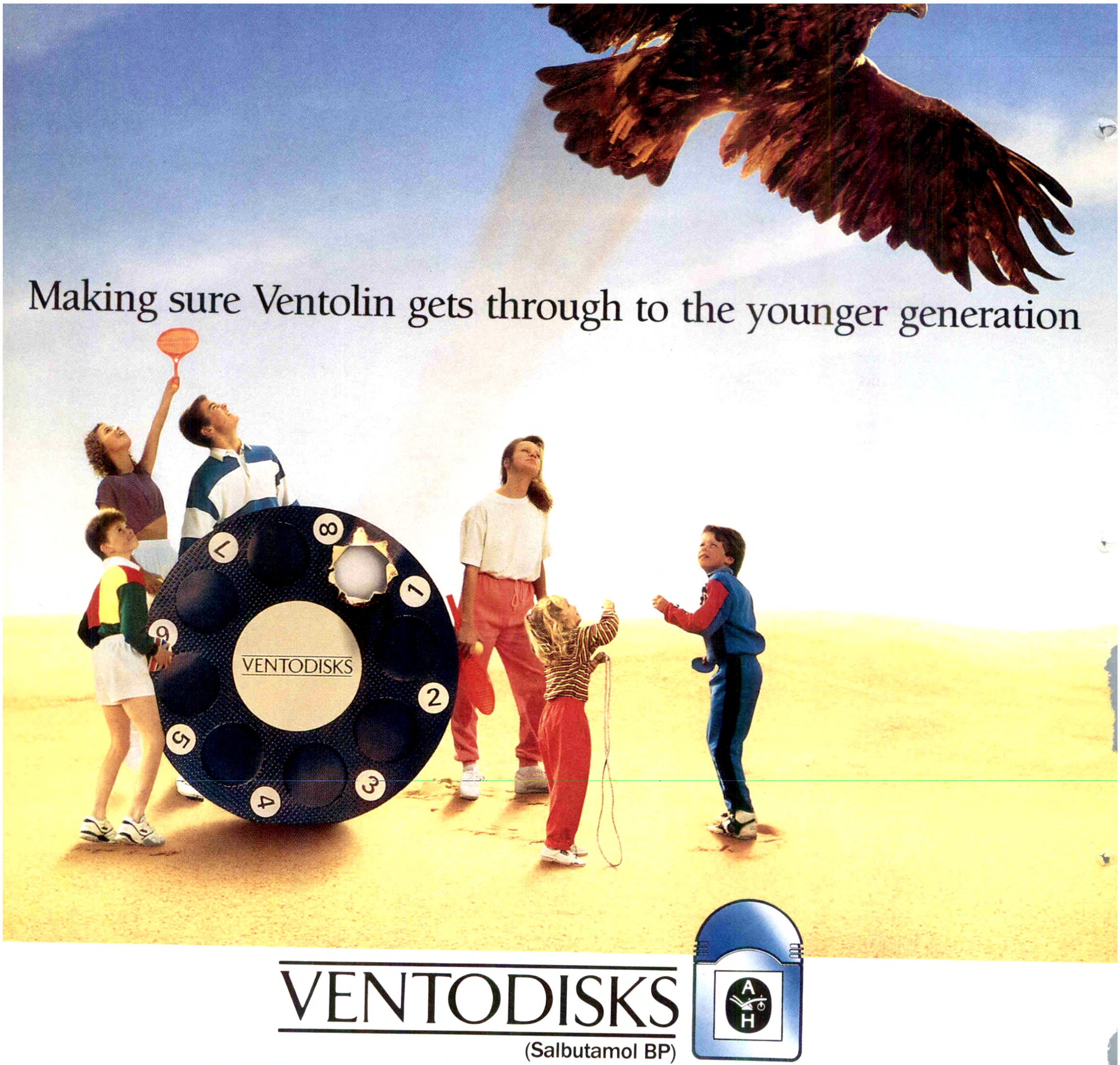
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ANNOTATIONS

Gastro-oesophageal reflux and the lung

Numerous reports in recent years have described the association of gastro-oesophageal reflux with respiratory symptoms, both among children being treated for gastro-oesophageal reflux and in those presenting with lower respiratory tract symptoms or apnoea. These studies, recently reviewed by Orenstein and Orenstein, have tended to focus on small, highly selected groups of children, and raise important questions concerning the nature, scale, and clinical implications of the associations observed, particularly during infancy.[1]

Despite intensive research interest in the pathophysiology of gastro-oesophageal reflux,[2] the development of methods for its detection,[2 3] and the elucidation of mechanisms of pulmonary dysfunction resulting from it,[1 4] the answers to many of the questions remain incomplete. This annotation highlights certain controversial areas and outlines an approach to the evaluation of children with respiratory symptoms and suspected gastro-oesophageal reflux.

Gastro-oesophageal reflux in 'normal' infants and children

It is well known that possetting occurs in otherwise healthy infants without respiratory or other alimentary symptoms. The development of sophisticated techniques for the investigation of gastro-oesophageal reflux, particularly 24 hour oesophageal pH monitoring, has led to its detection in completely asymptomatic infants.[2 5 6] As some gastro-oesophageal reflux is a normal occurrence, attempts have been made to define 'abnormality' in terms of the amount (volume or duration) of reflux and its pattern in relation to feeding and behavioural state.[7 8] Unfortunately, because of ethical constraints, the 'normal' populations studied have often been small with a wide age range and may not have been completely healthy. The 285 infants studied by Vandenplas and Sacre-Smits provide the largest available collection of 'normal' results for 24 hour oesophageal pH studies.[5] The upper limits of normal derived from these are higher than other published values,[6] however, and overlap with the results of symptomatic patients studied by other groups.[2 9]

The difficulty in defining 'abnormal' gastro-oesophageal reflux is a major problem when considering its relation to respiratory symptoms.[1] Although some studies suggest that nocturnal reflux may be important in determining respiratory symptoms[8] or apnoea,[10] it has not been possible to define patterns of gastro-oesophageal reflux which occur only in children with these symptoms. An excess of gastro-oesophageal reflux during sleep may also be found in infants and children without symptoms of lung disease or apnoea or objective evidence of pulmonary dysfunction.[7 11] Conversely, subjects with pulmonary symptoms may not have demonstrably 'abnormal' gastro-oesophageal reflux,[1 12] even when antireflux treatment improves these symptoms.[9] In certain children the response to gastro-oesophageal reflux, even when 'normal' in amount, may be the key event. In this situation any reflux might be potentially harmful.

The coexistence of gastro-oesophageal reflux and respiratory symptoms

The finding of 'significant' gastro-oesophageal reflux in a child with respiratory symptoms, or conversely respiratory symptoms in a child shown to have gastro-oesophageal reflux, may occur by chance, as a manifestation of a disorder affecting both gastrointestinal and respiratory systems, or as a cause and effect relationship. Gastro-oesophageal reflux might be responsible for pulmonary dysfunction or vice versa, or both might apply.

One way to support the contention that gastro-oesophageal reflux causes respiratory disorders is to demonstrate that its successful treatment alleviates respiratory symptoms. The natural history of gastro-oesophageal reflux, respiratory symptoms, and apnoea is to improve, particularly in infancy,[13 14] so that ideally the response to active treatment should be documented objectively and be followed by the recurrence of both gastro-oesophageal reflux and the original symptoms after withdrawal of treatment. The latter is impossible after surgery and has only rarely been reported with medical treatment, usually because parents had discontinued medication against advice rather than as part of a controlled study.[11 12] Although improvement in gastro-oesophageal reflux on treatment has usually been documented, pulmonary function has seldom been assessed, reliance being placed on symptomatic improvement as evidence of success.

There is, nevertheless, considerable circumstantial evidence that treatment of gastro-oesophageal reflux reduces respiratory symptoms in selected groups of patients, particularly those with recurrent pneumonia.[1 9 11 12 15] The evidence is less convincing in asthma where improvement, if it occurs, has tended to be measured by a reduction in the use of asthma medication rather than by abolition of symptoms.[9 15] When infants have suffered multiple, frequent apnoeic episodes that cease after adequate medical treatment or surgery it is difficult to remain sceptical about the underlying importance of gastro-oesophageal reflux.[14 16] This pattern is only observed, however, in a small proportion of infants who present with recurrent apnoea.

No studies in childhood have tested the proposition that treatment of respiratory symptoms might relieve gastro-oesophageal reflux, although theophyllines and β sympathomimetics may exacerbate it.[1] In adults there are conflicting reports of the effect on gastro-oesophageal reflux of asthma induced by bronchial challenge. Both a reduction[17] and an increase[18] in gastro-oesophageal reflux have been reported. Although large swings in intrapleural pressure induced by respiratory efforts have been thought to favour increased gastro-oesophageal reflux,[4] there is little evidence that this actually occurs and increased diaphragmatic work has also been thought to improve lower oesophageal sphincter competence.[19]

A cause and effect relationship can also be inferred from a temporal relationship between respiratory changes and gastro-oesophageal reflux. Clinically this has been demonstrated in individual children with stridor, wheeze, and apnoea both with natural and simulated gastro-oesophageal reflux,[1 8 16 20] although no temporal relationship has been found in larger groups of infants with apnoea.[1 20] In many studies in adult asthmatics, and some in children,[21] gastro-oesophageal reflux has been simulated (by introducing acid into the oesophagus) while monitoring respiratory function. Increased bronchial reactivity has been found in a proportion of such cases, usually those who also have heartburn.[1 21]

Mechanisms by which respiratory symptoms may result from gastro-oesophageal reflux

Respiratory symptoms resulting from gastro-oesophageal reflux could be caused by aspiration or by the stimulation of vagal nerve endings in the oesophageal mucosa.[1 4] In animal studies a stronger vagal response has been elicited with small amounts of acid in the trachea than by large amounts in the oesophagus. Microaspiration has therefore been postulated to explain the clinical association.[4]

The presence of a vagal response inducing bronchoconstriction has been inferred from the studies with simulated gastro-oesophageal reflux described above. There is, as yet, no satisfactory explanation for the difference in reaction between individuals or the occurrence of symptoms after some but not all episodes of reflux. This unpredictability is also true when aspiration is suspected though sometimes the link between reflux and respiratory symptoms is clearly demonstrated, for example, in infants or children with tracheo-oesophageal fistula, neurological damage, or coma.

Even when aspiration is suspected clinically as the cause of recurrent pneumonia it has been demonstrated in at most 25% of such cases by radioisotope scan.[1 3 22] It has also been detected in 20% of 'near-miss SIDS' cases in the absence of lower respiratory tract signs,[22] but not yet in children with recurrent wheeziness. This low incidence of detected aspiration could mean that its contribution to the causation of respiratory problems is small, or that aspiration is infrequent even when it is the cause, or that the sensitivity of the technique for detecting aspiration is poor. Other methods of detecting aspiration, such as the presence of fat laden macrophages in tracheal aspirates, are available but may not be sufficiently specific to be useful.[23]

Clinical evaluation of the child with respiratory symptoms and suspected gastro-oesophageal reflux

Clearly, infants and children with symptoms suggestive of gastro-oesophageal reflux should be investigated and treated irrespective of coincidental respiratory symptoms. In those with respiratory symptoms, a careful history and clinical examination is the starting point for assessment. Gastro-oesophageal reflux should be considered when symptoms are persistent, especially in children with recurrent pneumonia and those in whom choking has been troublesome. It should also be considered in children with poorly controlled asthma who have appreciable nocturnal symptoms, recurrent changes on radiography, or unexplained severe exacerbations.

A barium swallow may be helpful in demonstrating swallowing incoordination or a structural lesion but it is not a good method for diagnosing gastro-oesophageal reflux.[1 2] The search for gastro-oesophageal reflux should include a 24 hour oesophageal pH study and, if negative, a radioisotope scan, during which evidence of aspiration should also be sought. Although, as discussed above, a negative scan does not exclude aspiration, a positive result from a careful study is reliable evidence of aspiration.

'Significant' gastro-oesophageal reflux should be diagnosed if the pH study result, as a whole or in particular time periods, exceeds the published normal results collected from a relevant age group with the technique most closely resembling that used, if sufficient local normal results are not available. Radioisotope studies are usually considered positive if any reflux is seen, although this may be too non-specific an approach, particularly in infants.[2 3] Children with positive results should be treated in the hope that respiratory symptoms will subside but in particularly severe cases, especially with a suggestive history, it may be worth trying antireflux treatment even for 'normal' amounts of gastro-oesophageal reflux.

In young infants the thickening of feeds and prone anti-Trendelenberg positioning may be sufficient antireflux treatment. An alginate containing antacid like Gaviscon (Reckitt and Colman) and the gastrokinetic agent cisapride may be useful but the side effects of metoclopramide limit its role and bethanecol may exacerbate bronchospasm.[1] As no medical treatment is totally satisfactory and the individual response is so variable, changing or combining treatments can sometimes effect improvement. At present surgery is the only uniformly reliable method for eliminating gastro-oesophageal reflux and this is justified, after failure of medical treatment, when the symptoms are severe and there is good evidence that gastro-oesophageal reflux is relevant.

In conclusion, there is little evidence that respiratory disease per se causes gastro-oesophageal reflux, though its treatment may. The prevalence of 'abnormal' gastro-oesophageal reflux in children with respiratory disorders and its relevance when found are not fully known. Effective treatment of gastro-oesophageal reflux in such cases may result in a decrease in respiratory symptoms. Even 'normal' amounts of reflux may be a potential problem in individuals in whom there is a close temporal association between gastro-oesophageal reflux and respiratory symptoms, meriting a trial of antireflux treatment. The development of more effective medical treatment of gastro-oesophageal reflux and the wider application of objective means of assessing respiratory outcome would allow better definition of the contribution of gastro-oesophageal reflux to the causation of recurrent or chronic respiratory symptoms in infants and children.

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Investigation of rectal bleeding

The passage of blood through the rectum by a child often causes considerable parental anxiety. Unlike the situation in the adult,[1] however, the causes are often transient, almost invariably benign, and usually simply treated. Occasionally the blood indicates serious underlying pathology, and to avoid delay in detecting this possibility a positive diagnosis should be sought at initial presentation and may be found in most cases.

The age of onset clearly relates to certain diagnoses: necrotising enterocolitis and malrotation in the premature baby and neonate, anal fissures and intussusception in the young infant, and lymphoid hyperplasia and inflammatory bowel disease in the older child. Classification of aetiology of bleeding through the rectum is therefore usually based on age groups.[2]

A good history may lead directly to diagnosis. Passage of a firm stool, streaked with red blood (haemotochezia) and accompanied by anal pain is pathognomonic of anal fissure—a common problem. The child may be aware of 'something coming down' suggesting a rectal polyp or rectal mucosal prolapse. The dietary history may suggest features of intolerance (for example, cows' milk) leading to inflammation and bleeding.[3] The colour and amount of blood, its relation to stool, and the presence of abdominal or anal pain all point to the anatomical location of bleeding. Though melaena suggests an upper gastrointestinal haemorrhage, brisk bleeding from oesophageal varices, duodenal ulcer, or Meckel's diverticulum may result in passage of red blood. The possibility of bleeding due to a diathesis (von Willebrand's) or systemic illness (haemolytic uraemic syndrome, connective tissue disorders, Henoch-Schönlein purpura) should be considered and a detailed family history (familial polyposis coli) and drug history (non-steroidal anti-inflammatory agents, steroids, salicylates) is important. Bleeding due to stress ulceration should be considered in association with posterior fossa tumours,[4] burns, and cardiac surgery. Confirmation of the presence of blood by the examination of stool or nappy is important and, if doubt exists about whether stool contains blood, a faecal occult blood test should be performed.[5]

Examination centres on abdominal, perianal, and rectal findings together with inspection of stools, but a complete examination is needed to pick up clues. Cutaneous haemangioma may point to gastrointestinal haemangiomata. Buccal and lip pigmentation is classical with Peutz-Jegher polyposis. Petechial rash on buttocks and legs may not have been noticed by the parents of the child with Henoch-Schönlein purpura. Relevant abdominal findings include hepatosplenomegaly (cirrhosis and portal hypertension), mass (duplication cyst or intussusception), distended or thickened bowel (Crohn's disease, ulcerative colitis), and peritonism (inflamed Meckel's diverticulum or infective causes).

Anal and rectal examination is best conducted with the child lying either supine with hips and knees fully flexed or in the left lateral position (for a right handed examiner). The reassurring presence of parent or nurse holding the child, a sympathetic explanation to the child, and a calm and gentle approach normally permits full and detailed examination provided the child has not previously been hurt or frightened by rough or rapid examination. Careful separation of the buttocks and eversion of anal mucosa may reveal a fissure in the common posterior position. An anterior fissure is sometimes found when the anus is in an anterior ectopic position and slightly stenotic: further investigation and management will be needed. Fissures may be red and painful if acute or white and indurated if more chronic and inactive. Associated skin tags raise the suspicion of Crohn's disease. If the child can be persuaded to strain (a difficult manoeuvre for most children) an anal mucosal prolapse may appear. Prolapse of the complete rectal wall (procidentia) is usually related to significant underlying disorders (for example, cystic fibrosis or neurological disorders).

Digital rectal examination may be resisted (and also be unnecessary) if there is an anal fissure but otherwise is mandatory; its omission leads to missed diagnosis or unnecessary investigations. Rectal polyps (usually simple and solitary) may be palpated by sweeping the examining finger circumferentially round the rectal lumen until the polyp reaches the limit of mobility on its pedicle: the polyp may be prolapsed through the anus and even removed by avulsion by this manoeuvre. Pelvic intra-abdominal masses (duplication cysts, lymphosarcoma) may be identified by bidigital palpation. The appearance of blood, mucus, or pus on the examining finger indicates inflammatory bowel disorder.

If an infective cause is thought likely stools should be examined promptly; aerobic and anaerobic cultures and microscopy for ova and parasites are necessary. *Escherichia coli*, shigella, salmonella, campylobacter, and giardia all produce bloody diarrhoea. Severe bleeding due to cytomegalovirus colitis in a child with AIDS has recently been described.[6]

Whether sonography, radiography, or endoscopy is the first investigation depends on the suspected diagnosis, the expected yield of investigation, and whether or not general anaesthesia would be needed for endoscopy. Plain radiography and sonography are less invasive and distressing for a child and may give definitive information: a classical appearance of multiple short fluid levels in the right abdomen in a neonate with volvulus or the appearance of an intraluminal mass on sonography in a case of intussusception. Barium enema contrast radiography will give detailed information on the mucosal pattern and intraluminal lesions in the large bowel provided adequate preparation has been undertaken. Double contrast radiography gives better definition of intraluminal lesions.

The value of information obtained from proctoscopy, sigmoidoscopy, or colonoscopy relates to the experience of the observer, the degree of cooperation of the child, and to the success of bowel preparation. Even the most experienced observer will find examination of a squirming, anxious child with a loaded rectum inconclusive and preparation by fluids only, orally for 24 hours, oral sodium picosulphate, bowel wash out, and effective sedation or general anaesthesia are often necessary. In the newborn, the rectal mucosa can be seen using a small auriscope and the appearance of the inflamed and oedematous mucosa in necrotising enterocolitis may be recognised. Abnormal mucosal appearances may be quite characteristic[7]; hypertrophy, ulceration, and contact bleeding together with blood, mucus, or pus in the lumen strongly suggests Crohn's disease or ulcerative colitis. Lymphoid hyperplasia produces a nodular but intact mucosa. A biopsy specimen (by rectal suction or colonoscopy forceps) may give confirmation. Eosinophilia is noted with milk allergy.[8]

Full colonoscopic examination requires considerable expertise and the relative infrequency of indications in childhood impedes its acquisition by paediatricians and paediatric surgeons. Using a standard paediatric colonoscope, the lumen to the level of the splenic flexure can reliably be visualised, but transverse and ascending colon are not so easy. Young children may present additional challenges to technique.[9] Indications for colonoscopy are severe bleeding, moderate but persistent bleeding with negative barium double contrast enema findings, or a lesion of unknown nature seen on barium enema. A biopsy specimen of abnormal areas of the mucosa may be taken. Polyps may be snared and removed using diathermy. Bleeding points may be controlled by electrocautery, laser irradiation, or heater probe.

When bleeding persists but the source cannot be defined by conventional radiology and endoscopy the use of either radionuclide studies or angiography can be considered. Technetium sulphur colloid scan will detect ectopic gastric mucosa in a Meckel's diverticulum, though it may give false negative results in the presence of active bleeding. Technetium labelled red cells will accumulate in the bowel and will pinpoint a bleeding area provided the bleeding rate is greater than 0·5 ml/minute but do not define the cause of bleeding. Angiography can define the site and display the vascular picture of a haemangioma provided bleeding is fairly brisk (1 ml/minute). Intra-arterial digital subtraction angiography may add further definition. In difficult cases, depending on local expertise, computed tomography (for duplications and haemangiomata) and magnetic resonance imaging (for inflammatory disorders, necrotising entercolitis, bowel wall haematoma) may give useful information, though their roles are not yet clearly defined.[10]

In dire circumstances laparotomy may be necessary in the absence of a firm diagnosis. Techniques such as combined endoscopy and laparotomy, extensive transillumination of gut and mesentery, multiple enterotomies, and injection of methylene blue may help in the search for the bleeding point. Small bowel resection and anastomosis for bleeding Meckel's diverticulum and colectomy for inflammatory bowel disease may be life saving. Very occasionally small bowel tumours (lymphosarcoma, leiomyosarcoma) may be discovered.

When an episode of bleeding through the rectum has been mild and self limiting, when the history has revealed no clues, and examination has proved negative, however, it is reasonable to defer investigation until a second bleed in view of the significant proportion of cases in which all investigations will prove negative.

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Conventional allergy tests

Three common problems are whether symptoms are related to allergen exposure, whether a condition will improve if allergens are avoided, and the identification of which allergen (if any) was responsible for a specific exacerbation or adverse event. Are allergy tests any use?

Skin prick tests

The principle of prick tests is that the weal and flare reaction to an allergen introduced into the skin demonstrates the presence of mast cell fixed antibody, mainly IgE antibody.[1] Major problems include:

- A lack of agreed definition as to what constitutes a positive reaction[2]
- Positive tests in subjects without symptoms[2–5] (a few with positive skin prick tests do develop symptoms later, but as the test cannot identify this subset such information is of little value)
- Positive tests persisting after a child has grown out of allergy[6]
- Negative tests in some patients with genuine allergies—for example, up to 17% of patients with pollen induced rhinitis or asthma[7 8]
- The fact that prick tests fail to detect non-IgE mediated allergic reactions—for example, some reactions to cows' milk protein[9]
- Differing potency of allergen extracts[1 10]
- Errors due to poor technique, through delegation to untrained staff, the use of non-standard (for example, hypodermic) needles, or placing tests too close together (resulting in non-specific weal reactions).

Intradermal testing

Intradermal tests, which carry a small risk of fatal anaphylaxis, are far more sensitive than skin prick testing,[1] and hence produce more false positive reactions.[5 11]

Serum IgE antibody concentration

There are a number of laboratory methods, of which the best known is the radioallergosorbent (RAST) test.[10] Serum IgE assays are slightly less sensitive than prick testing, but clinical interpretation of results is subject to the same caveats and pitfalls as prick testing.[10] Unlike prick tests they can be informative where antihistamines cannot be discontinued, in the presence of dermographism, or with widespread atopic eczema.

Challenge tests

(A) INHALATIONAL

The aim is to provoke symptoms directly by delivering an allergen direct to a target organ (for example, lung or nasal mucosa). Difficulties include:

- Dose (high doses may give false positive result[1])
- Problems with particle size (for example, pollen grains may fail to cause bronchoconstriction because the grains (20 to 30 µm) are trapped in the nose and do not reach the bronchi; on the other hand, pollen extract (1 to 2 µm droplets) can give bronchoconstriction even in hay fever patients who are never troubled by asthma in the pollen season)
- The laboratory conditions may fail to replicate natural exposure—a provocation test may expose the airway to a total allergen dose which corresponds to exposure for days or weeks during the pollen season[1]
- Result may depend on non-specific reactivity reflecting the state of the underlying disease.

(B) BY INGESTION

As the end points are often less clear cut, food challenges may need to be performed double blind.[12] In practice there are a number of difficulties:

- Observation needs to be long enough to detect delayed reactions (up to 48 hours or more after ingestion[13])
- Standard methods with encapsulated dried foods (up to 500 mg per capsule) may not deliver an adequate dose; in some cases of food intolerance reactions occur only with larger doses[13]
- The state of the food may be important, with reactions occurring only to either the raw or to the cooked form[14]
- A challenge performed during a quiescent phase of the disease may fail to provoke an adverse reaction[14]
- Some adverse reactions occur only in the presence of other factors (for example, after exercise, after taking aspirin, or in the presence of other allergens) which if omitted result in a false negative test.[14]

Value of allergy tests

Tests for specific IgE antibodies, whether in the skin or the circulation, are of doubtful use, mainly because of the large number of false positive and false negative results. Textbooks acknowledge that test results can be interpreted only in the light of the history,[5] yet it is illogical to accept a result only if it fits with the history. Inhalational provocation tests are not generally available and are mainly of use as a research tool. The best approach is a careful history to look for clues to specific allergens, and trials of empirical avoidance measures where the condition is not easily controlled with simpler measures.

Food intolerance can be due to a number of mechanisms, only some of which are immunologically mediated. Skin and RAST tests are thus predictably unhelpful, with negative results in those with non-IgE mediated disease[9] and a large number of false positive results, including subjects who have outgrown their intolerance.[6] Subject to a number of limitations,[14] double blind challenges are a useful research tool. In routine practice, avoidance of items chosen from the history or from knowledge of frequent offenders,[15] followed by relapse after open challenge, is often sufficient intervention.

Conclusion

Until tests for IgE antibodies, whether in skin or blood, can be validated in clinical practice, their use is difficult to justify except as a placebo investigation or as a research tool; a trial of antigen avoidance is the most logical approach. The diagnosis of food intolerance is complicated by its heterogeneous nature, and a trial of avoidance followed by food challenge is the best available method. The lack of reliable conventional allergy tests is one reason for the current popularity of more unorthodox approaches.[16]

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Job sharing

Despite being a relatively new concept in medicine, job sharing provides an ideal solution for men and women who need to train and work part time in order to combine domestic commitments with the continuity of a career.[1] Clearly an openness to new concepts in employment will be increasingly necessary if highly qualified and experienced staff are to be attracted to stay in busy hospital specialties, particularly as nearly 50% of medical graduates are now women. Successful job sharing schemes have been undertaken in all post-registration hospital grades, general practice, nursing, and management.[2–9]

The table shows the numbers of hospital doctors in paediatrics who work on a full or part time basis. Of these, only four pairs have shared posts to our knowledge.

There are three ways in which part time posts may be created. The first is the conversion of an existing full time post to part time, this being rarely acceptable to the service or to colleagues. Secondly, supernumerary part time posts can be arranged with the help of regional postgraduate deans. At senior registrar level candidates apply for the PM(79)3 scheme[10] which has been in progress for 10 years. Training application having been approved by the regional postgraduate dean, the candidate is referred to a national appointments committee, short listed, and then required to attend for interview, held only once a year. At present there are fewer than 10 posts in paediatrics annually appointed on the PM79(3) scheme, and regional funding is not always available for successful candidates. This scheme is of no help to those seeking part time consultant appointments. The third option, and the subject of this annotation, is to share a full time post.

The advantages of job sharing include the opportunity of applying for full time posts thus increasing the choice of jobs available. Having two sets of experience and background brings a broader base to patient management. There is greater flexibility in duty rostering. Shorter breaks in cover occur due to holiday or sickness, as the other sharer is there at least half of the week. The unexpected bonus to the sharing of problems and management is the reduction of the stress of uncertainties and in the feelings of isolation so often encountered in clinical practice.

Paediatric hospital doctors including paediatric neurology, DHSS review (England and Wales) 1987

Grade	*No of doctors*	*Whole time*		*Part time (%)*	
		Men	*Women*	*Men*	*Women*
Registrar	303	159	92	3 (1)	13 (4)
Senior registrar	171	64	25	0	18 (11)
Consultant	675	390	104	58 (9)	33 (5)

There are some potential problems. Both candidates must be first choice at the job interview in order to be competitive. Different backgrounds could lead to a potential difference in time to accreditation or retirement. Unlike the PM (79)3 scheme for higher specialist training the post is not designed specifically for the individual. Incompatibility is minimised by a joint commitment to making the job share work.

The administrative details of job sharing are easily manageable. The contract essentially means that working hours, pay, and holidays are divided equally. With the Pay As You Earn system, deductions for national insurance and superannuation are made as a straightforward percentage. The cost to the hospital is the same for two job sharers as for one person. If one person leaves the other is still under contract. The remaining partner may choose to take up the post full time, to work with a further part time replacement, or alternatively resign. A significant security came about in November 1988 when the Medical Manpower and Education Division of the Department of Health and Social Security confirmed that at senior registrar level, job sharers are considered eligible for the PM(79)3 scheme in the event of the job share breaking down (personal communication).

The keys to a successful job share partnership are mutual trust, loyalty, flexibility, and a commitment to each other as well as to excellent patient care and specialist training. Impeccable handovers are vital and must cover all responsibilities of the job. Optimal handovers should be in both verbal and written formats. Clear and full completion of patient casenotes provides clarity both for the job sharer and other medical colleagues. Outpatient follow up appointments can be calculated to provide continuity of care with the respective sharer. Handovers should include particular mention of problem outpatients. Availability by telephone is helpful and we spend approximately one hour a week in such discussion. Due consideration must be given to the division of the working week. For junior staff, a block of work may give better continuity of care for inpatients and reduces the handover exercise to once a week. Other staff, including switchboard operators, need to know clear details of the working arrangement. A shared bleep may simplify communications. The on call commitment is normally split, each job sharer working half the on call of full time colleagues. An informal agreement to cover each other's domestic emergencies may be helpful. At consultant level committee work and teaching can also be shared.

A greater acceptance of the scheme will lead to its wider application particularly at consultant level. Some consultants may need to reduce activities when approaching retirement or when faced with personal disability or significant commitments outside medicine.

There is a job share register organised on behalf of the British Paediatric Association by one of the authors (RJ). It must be appreciated that many people seeking part time work are not only limited in their available time, but are often also restricted geographically and this may severely limit the workings of a register unless it is quite sizable. At training level this problem could be reduced if there was sufficient flexibility in the system to allow for example a senior senior house officer and a registrar, or a registrar and a senior registrar to share the same post. We fear that the system for allocating registrar and senior registrar posts is likely to become more rigid under the recommendations found in the consultative document *Hospital Medical Staffing: Achieving a Balance.*[11] Furthermore there is nothing to suggest, so far, that with the greater autonomy envisaged under the white paper regional health authorities will respond more flexibly to the training needs of their junior staff.

It is to be hoped that manpower planners will significantly increase opportunities for part time or shared training and career posts if the many women graduates with young families are to be persuaded to remain in acute hospital specialties. Such schemes must be made known to students and new graduates before career choices are fixed.

We are convinced from our personal experiences that job sharing does work at training or consultant level and that it enables us to maintain enthusiasm and balance in our working and personal lives.

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11 UK Health Departments, Joint Consultants Committee, Chairmen of Regional Health Authorities. *Hospital medical staffing: achieving a balance—plan for action.* London: HMSO, 1987.

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ORIGINAL ARTICLES

Factors influencing the outcome of congenital heart disease detected prenatally

Gurleen K Sharland, Susan M Lockhart, Sunder K Chita, Lindsey D Allan

Abstract

The diagnosis of structural heart disease before birth is associated with a poor prognosis. Of 222 continuing pregnancies seen in a 10 year period, there has been a 79% mortality. This is inconsistent with published results and current concepts of the outcome for children with cardiac malformation. Of the 222, death occurred in intrauterine life in 57, 87 died as neonates, and 31 in infancy or childhood. There are 47 survivors of whom only five have survived beyond 4 years.

Factors influencing the outcome in these cases were examined further. A high mortality was associated with the presence of extracardiac anomalies in 71 (32%) and prenatal cardiac failure in 28 (13%). As many patients were referred for these reasons, referral methods preferentially select patients with a different range of heart disease from that seen postnatally. In addition, some forms of heart disease progress in severity during fetal life. Those involved in the management and counselling after diagnosis of heart disease in early pregnancy must be aware of the additional prenatal factors influencing prognosis and allow for them in making predictions of outcome.

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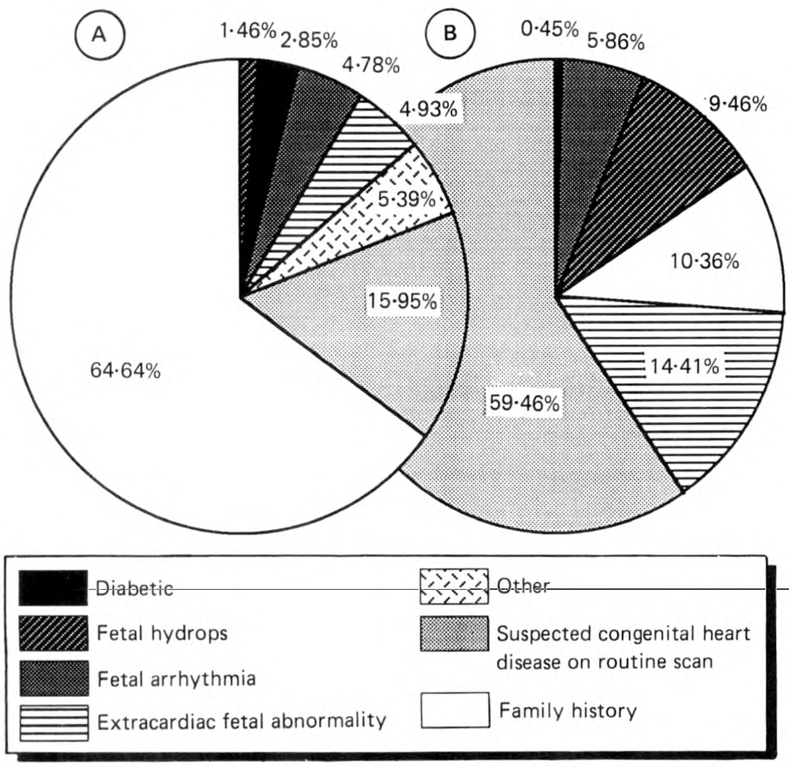

Figure 1 (A) Reasons for referral in 1298 pregnancies referred for fetal echocardiography in 1989. (B) Reasons for referral in study group of 222 cases of fetal congenital heart disease.

Over the last 10 years fetal echocardiography has become established as an accurate method of predicting structural cardiac malformations prenatally.[1,2] There has been a progressive increase in the number of cases referred for fetal echocardiography and a corresponding increase in the number of cases detected prenatally, but the outcome for congenital heart disease diagnosed in utero is poor. One of the main reasons for this is the high rate of termination of pregnancy after the detection of a severe cardiac abnormality. In our series of 442 cases of cardiac malformation diagnosed in utero, approximately 50% of cases resulted in a termination of pregnancy. Of 222 pregnancies that continued, however, the survival rate is still low with only 47 infants still alive (21%). In order to account for the high mortality, associated factors that might influence the outcome were analysed.

Methods

Between 1980 and the end of 1989 over 7000 high risk pregnancies were referred to our unit for fetal echocardiography. High risk factors include maternal reasons, such as a family history of congenital heart disease, maternal diabetes or exposure to cardiac teratogens in early pregnancy, or fetal indications such as the detection of hydrops, extracardiac anomalies, arrhythmias, or an abnormality of the four chamber view on a routine scan. The proportion of cases seen in each referral group during one year are shown in fig 1A. The gestational age at presentation varied from 16–40 weeks. A structural malformation of the fetal heart was diagnosed in 442 cases. After the detection of severe congenital heart disease, the pregnancy was electively ended in 220 cases and these cases are excluded from this study. In the remaining 222 cases the pregnancy continued and these form the study group. The referral reason was a suspected cardiac abnormality on four chamber view screening in 132, an extracardiac fetal abnormality in 32, a family history of congenital heart disease in 23, the presence of non-immune fetal hydrops in 21, a suspected fetal arrhythmia in 13, and maternal diabetes in one case. The proportions of referral groups in the abnormal cases are shown in fig 1B. The case records of all the patients were examined retrospectively. Videotape recordings of all the fetal scans were available for inspection. The type of cardiac lesion present in each case was recorded. Evidence of extracardiac structural and chromosomal anomalies seen either on the scan or detected subsequently on postnatal or postmortem examination were recorded for each case.

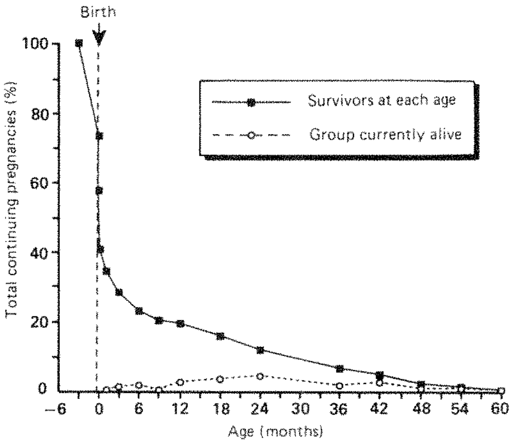

Figure 2 Time of survival after the diagnosis of prenatal congenital heart disease. The bold line shows the length of survival after diagnosis and the interrupted line shows the ages of the 47 cases that are still alive. The survival numbers are represented as a percentage of the total study group (222 cases).

Signs of intrauterine cardiac failure, which include fetal ascites, skin oedema, pleural and pericardial effusions, were sought on each scan.

Results

Of 222 continuing pregnancies, 57 resulted in a spontaneous intrauterine death. There were, therefore, 165 infants (74%) that were born alive and of these, 87 died in the neonatal period, 29 in infancy, and two in childhood. There are 47 cases that are still alive. The length

Table 2 Types of extracardiac structural abnormalities and chromosomal anomalies associated with congenital heart disease in the study group

Extracardiac anomaly	*Total No*	*No with associated chromosomal anomaly*
Exomphalos	12	5
Diaphragmatic hernia	7	2
Renal	5	1
Duodenal atresia	5	2
Oesophageal atresia	3	0
Anal atresia	1	1
Conjoint twins	4	0
Cystic hygroma	2	2
Multiple	3	0

those resulting in a neonatal death, 13% of those who died after the neonatal period, and 11% of those that are still alive. The types of associated extracardiac structural anomalies and chromosomal abnormalities are shown in tables 2 and 3. There was evidence of intrauterine cardiac failure in 28 fetuses (13%). Of these, 16 resulted in an intrauterine death, 10 resulted in a neonatal death, one case died in infancy, and one child survived. In 10 (5%) there was an extracardiac structural abnormality detected in addition to the cardiac anomaly but in the remaining 18 (8%) there was structural heart disease only. The incidence of fetal hydrops was particularly high (28%) in the group resulting in a spontaneous intrauterine death compared with the other groups (11% in the neonatal death group, 3% in the infant deaths, and 2% of the survivors).

A wide range of cardiac malformations were detected in the 222 fetuses and the diagnoses are

[redacted]

Table 3 Types of karyotype anomalies and outcome associated with prenatal congenital heart disease

Chromosomal anomaly	*Total*	*Outcome*			
		Intrauterine death	*Neonatal death*	*Infant (childhood) death*	*Alive*
Trisomy 21	14	5	3	1	5
Trisomy 18	16	3	12	1	0
Trisomy 13	5	3	2	0	0
Turner's syndrome (XO)	2	2	0	0	0
+9/10	1	0	1	0	0
13q−	1	0	1	0	0
8q−	1	0	1	0	0
−10	1	0	0	1	0
XXY	1	0	0	1	0

Table 4 Cardiac malformation and outcome in 222 cases of fetal congenital heart disease

Diagnosis	*Intrauterine death*	*Neonatal death*	*Infant (childhood) death*	*Alive*
Hypoplastic left heart syndrome	3	11	1	0
Mitral atresia, double outlet right ventricle	2	5	1	0
Aortic atresia	4	2	0	0
Critical aortic stenosis	4	10	1	0
Coarctation	6	5	4	3
Interrupted aortic arch	0	2	0	0
Ebstein's anomaly/tricuspid valve dysplasia	8	11	2	3
Tricuspid atresia	1	1	4	1
Pulmonary atresia	2	3	2	2
Tetralogy of Fallot	3	5	3	3
Absent pulmonary valve	2	2	1	0
Pulmonary stenosis	0	0	0	4
Atrioventricular septal defect	8	11	4	9
Ventricular septal defect	1	9	1	8
Common arterial trunk	0	1	3	0
Transposition of great vessels	0	0	0	3
Cardiomyopathy	6	2	0	5
Tumour	4	0	0	1
Other	3	7	4	5

nosis at presentation, poor growth of the left ventricle, aorta, and mitral valve was observed in sequential studies so that as gestational age advanced the echocardiographic features became those of a hypoplastic left heart. There were nine fetuses with an isolated ventricular septal defect who died in the neonatal period but these all had an associated extracardiac anomaly.

Discussion

It has been observed in many forms of congenital anomaly that prenatal diagnosis detects the most severe end of the range of disease and is therefore associated with a poor outcome.[3] This is also true for congenital heart disease. Cases referred for fetal echocardiography are specially selected and therefore produce a different range of disease than that seen postnatally.[4] The majority of cases in our series were referred because a cardiac abnormality was suspected on a routine obstetric ultrasound scan on examination of the four chamber view.[5] Thus, the more gross types of cardiac defect are seen and referred for further evaluation as a result of the four chamber screening programme. However, a number of patients were referred because of the detection of a non-cardiac structural abnormality (14·5%) or the presence of fetal hydrops (9·5%). Thus those with associated non-cardiac abnormalities are also being specially selected for referral.

The incidence of associated anomalies, in particular the karyotype anomalies, is higher in this series than expected. Chromosomal abnormalities in association with congenital heart disease have been reported to occur in about 12–13% of cases in postnatal series.[6] The overall incidence in our series of 222 cases was nearly 19%. This was particularly high in the group resulting in an intrauterine or neonatal death (21% and 24% respectively). The incidence in cases that are still alive or in those that died after the neonatal period, however, is similar to that reported postnatally (11% and 13% respectively). The chromosomal anomaly present in all the survivors is trisomy 21. The association between certain types of cardiac malformation and karyotype abnormalities has been previously described.[7–9] Atrioventricular septal defects are commonly associated with trisomy 21 and malalignment ventricular septal defects with trisomy 18. Many unexpected associations have been encountered in the prenatal range of congenital heart disease, however, so that it is an important part of management of all continuing pregnancies to obtain a fetal karyotype.

Cardiac malformations are generally thought to be well tolerated by the fetus yet in this series of 222 cases, 13% had evidence of intrauterine cardiac failure at presentation. Some of these had an associated extracardiac anomaly, which could account for the hydrops but two thirds of cases did not. In our series, only one of the cases that had fetal hydrops and congenital heart disease is still alive.

Most forms of major cardiac malformations have been diagnosed in utero. In some cases the initial diagnosis indicates a poor prognosis. However, progression of the cardiac lesion with advancing gestational age can occur, which can alter the prognosis in cases that may initially appear less severe. For example, valvular stenosis can develop during fetal life and this can progress to valvular atresia by term. Valvular incompetence can become more severe as commonly occurred in cases of tricuspid valve dysplasia and Ebstein's anomaly in our series. Reduced growth of cardiac structures during pregnancy can result in a different diagnosis at term compared with findings at an earlier gestation. This has been observed, for example, in cases of critical aortic stenosis progressing to the hypoplastic left heart syndrome and has been previously reported.[10] It can therefore be difficult to predict accurately the outcome of some forms of heart disease when seen early in pregnancy.

In conclusion, there are several factors influencing the outcome of congenital heart disease diagnosed prenatally. There is a high incidence of associated anomalies, which includes extracardiac structural anomalies, chromosomal anomalies, and intrauterine cardiac failure. It is therefore important to look for these in all cases. Severe cases are selected for fetal echocardiography as a result of the four chamber screening programme but even in less severe cases, progression of disease can occur in fetal life. This emphasises that the range of heart disease seen prenatally is different from that seen postnatally and this is reflected in the outcome of cases diagnosed in utero. Those involved in counselling in early pregnancy must be aware of the additional prenatal factors and allow for them in making predictions of outcome. Thus the paediatric cardiologist faced with a fetus of 18 weeks' gestation with a particular type of congenital heart disease must consider several aspects before counselling the parents. Firstly, are there extracardiac or chromosomal anomalies present? Secondly, is intrauterine cardiac failure present or is it likely to develop? Thirdly, is there potential for evolution of the defect into a more severe form of disease? Fourthly, are there features of the defect that may not be detectable in early pregnancy but which will influence such factors as operability? Only when all these factors have been taken into consideration, or eliminated where possible, should a prognosis be offered.

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Preschool vision screening

S N Jarvis, R C Tamhne, L Thompson, P M Francis, J Anderson, A F Colver

Abstract

Although a good case for preschool screening for vision defects can be made there is very little evidence that existing programmes are effective in practice. A comparative trial of three different methods of preschool vision screening is described. Some 7000 children initially aged 5 months (younger cohorts) and 30 months (older cohorts) in three matched areas entered the trial during 1987. During 18 months of follow up new visual and ocular defects among these children were ascertained through ophthalmology outpatients and from optician records.

Screening at 35 months by an orthoptist based in the community is superior to conventional health visitor surveillance at 30 months and to an agreed programme of primary care screening for squint at 30–36 months as judged by screening sensitivity (100% *v* 50% *v* 50%) and the incidence of treated target conditions (17 *v* 3 *v* 5 per 1000 person years). A notable feature in the area served by the orthoptist is that 13 children received treatment for straight eyed visual acuity loss from among 1000 children whereas there were no such cases among 2500 in the comparison areas.

In the younger cohorts (that is, screening at age 5–9 months) all three programmes showed equally poor results, only one of the eight treated target conditions arising from all 3500 younger children being screen detected.

The early detection of squints, refractive errors, and amblyopia in childhood is desirable because of the critical requirement for a clear retinal image in the normal development of visual physiology.[1] In England and Wales 98% of all health authorities conduct preschool vision screening with the intention of early detection of such abnormalities, but do these programmes have the desired effect?[2]

The primary requirements for a screening programme are met,[3] insofar as vision and ocular defects represent common and serious disorders (affecting more than 2% of children by age 2),[4] which have at least partly understood natural histories[5 6] (including recognisable preclinical phases). There is also circumstantial evidence that early treatment of these disorders will produce benefit in terms of a reduced frequency and severity of permanent amblyopia.[7 8] There must still be doubts, however, about these benefits of early treatment in view of the excellent study of Ingram *et al*, which was unable to demonstrate any benefit from the use of glasses in children with severe refractive errors between the ages of 1–3 years.[9]

Is there then any evidence that preschool vision screening programmes are effective in practice? Encouraging results have been reported from trials of community screening by photorefraction[8] and by orthoptists.[10] A retrospective cohort study in Canada also suggested a reduction in poor vision outcomes of 50% after preschool vision screening using the 'illiterate E test'.[11] On the other hand, an evaulation in 1980 of a community programme relying on clinical medical officers, health visitors, and general practitioners, similar to that used throughout England and Wales, suggested that such preschool vision screening had virtually no effect on the diagnostic process.[12] There was also evidence in 1984 that 30% or more of important squints and refractive errors remained undetected until after the age of 5 years in a similar programme in Newcastle.[13] Recently Ingram reviewed the evidence and concluded that a 'screening programme at the age of 3·5 years was 'no more effective' than school screening 'in producing better results'.[14]

The issue is of particular relevance now, first because the Hall report has recommended that 'screening for vision defects in preschool children should be confined to history and observation',[15] second because of the movement of preschool surveillance away from health authority clinics to primary care, and third because of the competing claims of orthoptists[10] and opticians (through a national advertising campaign) to take on elements of this screening role.

A decision to pilot preschool vision screening at age 5 and 35 months by a community orthoptist in part of Newcastle upon Tyne (leaving the remainder of Newcastle with conventional clinical medical officer/health visitor/general practitioner screening) coincided with the implementation across the whole of adjacent Northumberland Health District of an agreed minimum set of screening procedures centred in primary care that included squint checks at 7–9 and 30–36 months.[16] There was therefore the opportunity for a comparative evaluation of three different preschool vision screening programmes on a prospective basis (the orthoptist pilot, the existing programme in Newcastle, and the new Northumberland procedures). This paper is a report of this evaluation after 18 months of follow up.

Methods

The objective was to compare the three prog-

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rammes in terms of (i) the rate of screening coverage of the population for which it was intended, (ii) the rate and timing of target condition identification in the whole population irrespective of the source of referral, and (iii) the performance characteristics of the screening tests among those who attended for screening (that is, sensitivity, specificity, and predictive value).

The target conditions for preschool vision screening were taken to be squints, and/or visual acuity loss (which might be due to refractive error or to amblyopia) confirmed by an

[redacted]

Two sets of data were collected about these children: the first about screening and the second about target conditions.

SCREENING DATA

For each cohort child the community child health clinic record (the MCW46) was examined to establish whether screening had occurred and to note any relevant referral data. Additional material was extracted from the routine quarterly returns made by the orthoptist for the pilot areas and this included data about children

The source of referral for each potential case seen in outpatients was determined from outpatient notes, MCW46 and orthoptist records, and where in doubt by direct inquiry from that child's health visitor. Such referral was attributed to screening only if there was evidence that it resulted from routine surveillance initiated by a professional at the appropriate age (that is, was preclinical).

Results

SCREENING DATA

Altogether 8600 MCW46 and orthoptist records were examined in some 24 clinics distributed across Newcastle and Northumberland. These represented 93% of the target populations in the different cohorts.

From the data extracted (table 2) it is seen that the coverage rates of 60–70% achieved by the orthoptist are similar to rates achieved in the comparison areas. The exceptions to this are the coverage rates of over 80% achieved by Newcastle health visitors for their examination of infants aged 9 months and by the Northumberland primary care teams for their examinations of children at 2·5–3 years of age.

A substantial proportion of those who attended for screening by orthoptists were asked to come again for review rather than being definitively assigned as positive or negative (6% of the younger cohort and 20% of the older cohort). Figure 1 shows that about one third of those called for review failed to attend. Furthermore the referral rate from those who are reviewed was at least three times higher than the primary screening referral rate. This raises the possibility of a substantial number of children who were screened once, and who might have needed referral but who failed to attend for review by the orthoptist. We have no equivalent data from the comparison areas.

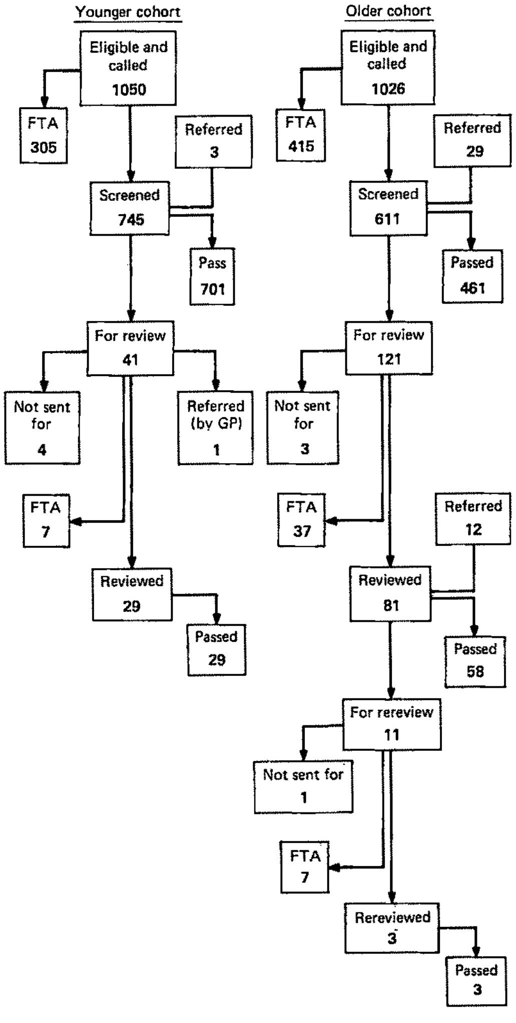

Figure 1 Process of screening by the orthoptist (from orthoptist records). FTA, failed to attend; GP, general practitioner.

OPTICIAN SCREENING AND CASES

A preliminary search of Northumberland* opticians' returns GOS(V) and GOS (ST) for one quarter of the follow up period (84 000 forms undifferentiated by age) showed only 16 cohort members who had received free sight tests but did identify three new children prescribed glasses. Opticians therefore hardly 'screened' this population of children, but they were seeing a number of cohort members with target conditions. These cases are 'treated' by opticians and may never come to the attention of hospital based eye services.

TARGET CONDITION DATA

A total of 138 potential cases of target conditions have so far been identified from the records of cohort members attending ophthalmology outpatients. These children were the 'incident' cases who were first referred after entry into the cohorts at age 5 and 30 months respectively. The ascertainment system also identified a large number of 'prevalent' cases in these cohorts (that is, children who had already been diagnosed with target conditions before entry into the cohort). A preliminary diagnostic assignment of the incident cases (fig 2) showed little difference between the three programmes for the younger cohorts but a striking difference in favour of the orthoptist programme for the older cohorts.

When comparing the number of cases arriving from areas with differing screening programmes, it should be recalled that the Newcastle comparison cohorts are up to 35% larger than the other cohorts (see table 2). This makes even more striking the excess of target conditions (both total and treated) arising from the older cohort in the orthoptist area (χ^2=42·0 and 24·3, df=2, p<0·001). Moreover, of the 26 older children with treated target conditions from the orthoptist area, half had straight eyed visual acuity loss† whereas no similar children have yet appeared from the comparison areas.

When considered from the perspective of the ophthalmologists the actual proportions of new

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*Newcastle (rather than Northumberland) opticians served the majority of the cohorts.

†Virtually all of these children had refractive errors and most were thought to be amblyopic. However the determination of amblyopia at this age is difficult.[9]

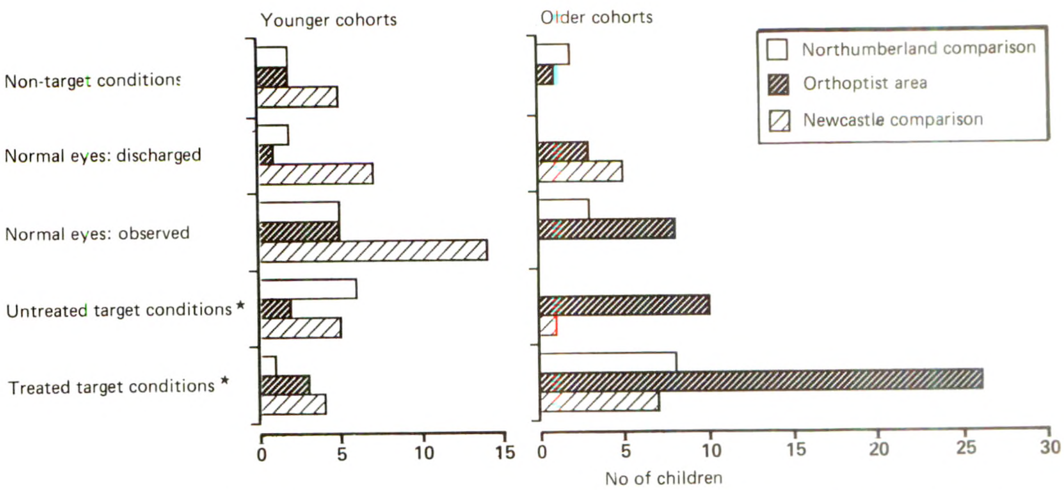

*Figure 2 Diagnoses of children from the three areas seen as new outpatients by ophthalmologists. *Squint, and/or visual acuity loss confirmed by an ophthalmologist.*

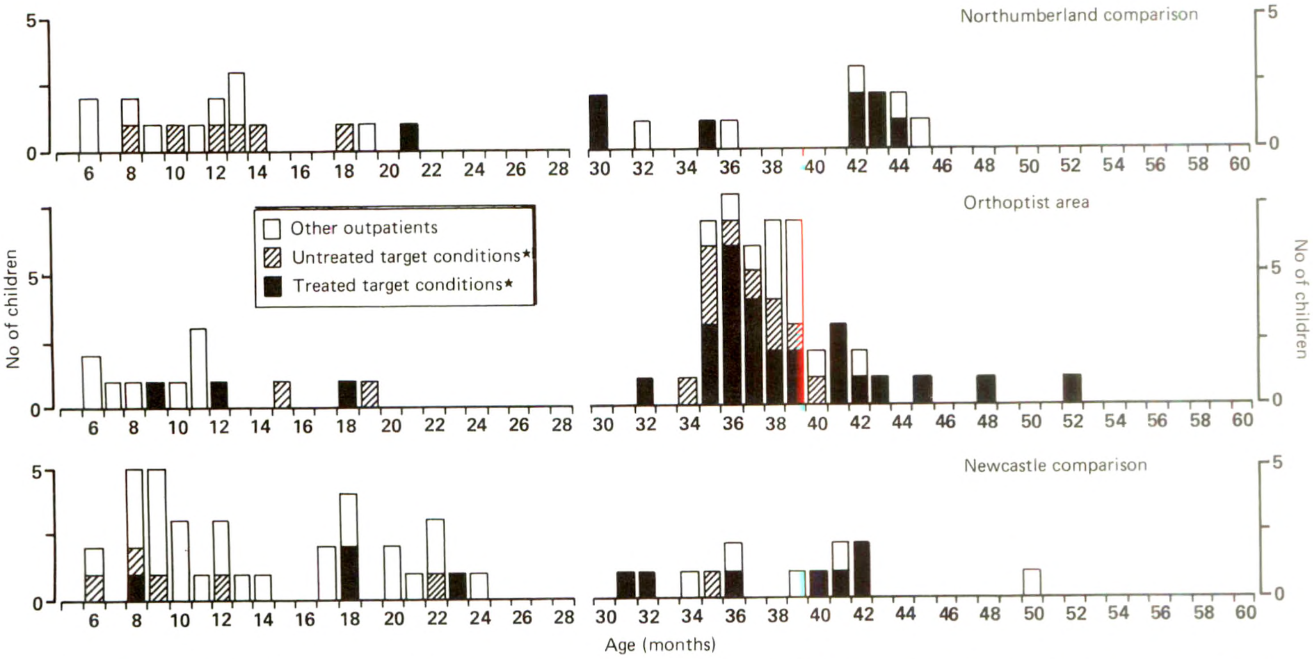

*Figure 3 Age of children from the three areas when first seen as outpatients by ophthalmologists. *Cases of squint and/or visual acuity loss confirmed by an ophthalmologist.*

outpatients appearing from the cohorts with 'correct' target conditions was appreciably different in the two age groups. Thus only a third of the children seen as outpatients from the younger cohort were actually diagnosed by the ophthalmologist as having a target condition and less than half of them in turn had entered treatment. On the other hand, for older cohort children, two thirds of new outpatients had the target conditions, of whom over three quarters entered treatment. It was also interesting to note among the younger cohort children seen in outpatients the relatively large number with 'normal eyes but to be observed'. It appeared that once a child under 1 year of age had been referred, some ophthalmologists were unlikely to discharge them as normal preferring to review them when they were older. This group should contract as follow up proceeds but meanwhile represent a substantial load on outpatients as well as potential anxiety to parents and children.

When the timing of the diagnosis of these outpatient cases was considered (fig 3) it was seen that although there was no significant difference in the mean age at diagnosis, there was a considerable surge of children with the target conditions of vision screening in the few months after orthopist screening at 35 months. This increase in cases was largely composed of children who went on to receive treatment.

CHARACTERISTICS OF THE SCREENING TESTS

Table 3 shows the routine health visitor contacts at 9 and 30 months in the Newcastle comparison area compared in more detail with screening by the orthoptist at 5 and 35 months‡. It was clear that vision screening in the younger age group

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‡There was insufficient data on the original source of Northumberland cases to use them in such an analysis. However it was clear that at least four of the eight treated target conditions in the older Northumberland cohort were false negatives at screening.

Table 3 Performance characteristics of preschool vision screening where correct=(a) any target condition and (b)=treated target conditions only (numerator/denominator)

	Sensitivity		*Specificity*		*Positive predictive value*	
	(a)	*(b)*	*(a)*	*(b)*	*(a)*	*(b)*
Younger cohorts:						
Orthoptist pilot area (5 month screen)	25 (1/4)	50 (1/2)	99·7 (739/741)	99·7 (741/743)	33 (1/3)	33 (1/3)
Newcastle comparison area (9 month health visitor check)	17 (1/6)	0 (0/3)	99·7 (1132/1136)	99·6 (1134/1139)	20 (1/5)	0 (0/5)
Older cohorts:						
Orthoptist area (35 month screen)	100* (28/28)	100* (21/21)	98·3* (570/580)	97·1* (570/587)	74 (28/38)	55 (21/38)
Newcastle comparison area (30 month health visitor check)	43 (3/7)	50 (3/6)	100 (807/807)	100 (808/808)	100 (3/3)	100 (3/3)

*Fisher exact two tailed probabilities of difference between orthoptist and comparison ≤0·01.

missed many of the target conditions irrespective of which programme does the screening. Meanwhile, false positive referrals from screening at 5–9 months were rare and no worse for the health visitors than for the orthoptists.

In the older cohort on the other hand no false negative cases have been detected so far after orthoptist screening at 35 months. Indeed three quarters of the 26 older children seen in outpatients with treated target conditions were referred from orthoptist screening. This sensitivity was perhaps at the expense of a slight lack of specificity (that is, increased false positive rate), though a positive predictive value of 74% must be considered good. By contrast, Newcastle health visitor surveillance at 30 months although very specific (that is, no false positives), missed over half of the small number of cases that have so far appeared in the screened part of this cohort.

Discussion

We present strong preliminary evidence for a beneficial effect from community orthoptist screening at age 35 months when compared with conventional health visitor surveillance or to specific attempts to detect squints in primary care. This finding has led to the adoption of such screening across the whole of Newcastle Health Authority.

By contrast we also present preliminary evidence for a lack of any beneficial effect of community orthoptist screening at 5 months of age. This practice has now been discontinued in Newcastle. The community orthoptist is still available to see children referred to her from this younger age group and will thus hopefully reduce the load of outpatient referrals from primary care.

There are some important reservations to be made concerning these conclusions. First the follow up is not yet complete. Further false negative cases may continue to appear in the screened cohorts but this would now seem to be unlikely to change the conclusion regarding relative screening sensitivity. However there is also the important question of the ultimate outcome of early treatment. The planned follow up of the cohorts extends for 2·5 years after their original recruitment (that is, until the age of 35 months and 60 months respectively) and as they reach these 'exit' ages the children become eligible for rescreening either by orthoptists (Newcastle younger cohort), by primary care teams (Northumberland younger cohort), or at school entry (Newcastle and Northumberland older cohorts). These occasions will be used as final opportunities to check the vision of the cohort children particularly in terms of amblyopia (that is, deficiency in visual acuity uncorrectable by refraction). It is only a demonstration of differences in the rates of amblyopic children between cohorts that will refute the proposition that all the treated target conditions in the older orthoptist cohort would have managed just as well with later (or no) treatment.

A second reservation is that the children presenting in eye outpatient clinics may not represent all the referred children for a number of reasons. For instance, when looking at the outpatient referrals arising from the different areas one must bear in mind the 'clinical' service offered by the orthoptist to local health professionals requiring an opinion on children of any age. This might have had two effects. Potential cohort children could have been seen by the orthoptist before the entry ages at 5 or 30 months and thus have compromised the original comparability of the cohorts (actually six visits with one onward referral). Alternatively this request service might have lowered the proportion of inaccurate outpatient referrals in the orthoptist area after the entry ages (84 visits with six older onward referrals). Not only does it seem therefore that the referral threshold for such an orthoptist opinion is low, but it also seems that a number of unnecessary outpatient referrals are avoided by this means. This may partly explain the excess of normal eyes and non-target conditions referred to outpatients from the younger cohort in the Newcastle comparison area where such a service was not available (fig 2).

A third qualification is that other potential outpatients in eye clinics may have been directed or self referred to opticians and may even have received treatment of refractive errors (one of the target conditions) entirely outwith the hospital service. We will ascertain such cases more completely towards the end of the follow up period by questionnaire to the families of cohort children. Meanwhile our pilot search of records from the family practitioner committees suggests that there are a number of such children but that because of the large numbers of such records this is an impractical source.

The final qualification to the outpatient data is that there are some children who are referred but never appear in outpatients. Of a total of 44 referrals from orthoptist screening (see fig 1) three have not been traced as outpatients. We have no equivalent data so far on screening referrals from the comparison areas.

PREVIOUS EVALUATIONS OF PRESCHOOL VISION SCREENING

The only similar comparative evaluation which we have been able to find in the literature is that [redacted]

trial of photorefraction at 6–9 months does not attempt to compare this with other methods of younger preschool vision screening, but is rather concerned to demonstrate the efficacy of early treatment by controlled trial.[8] Their screening coverage rates at 71% are remarkably similar to ours (see table 2) and the yield in terms of squints detected at screening was also comparable.

PRACTICAL IMPLICATIONS FOR THE EVALUATION OF SCREENING

There are two further issues in the evaluation

land for permission to examine their records. This research is supported by a grant from the locally organised research scheme of Newcastle Health Authority.

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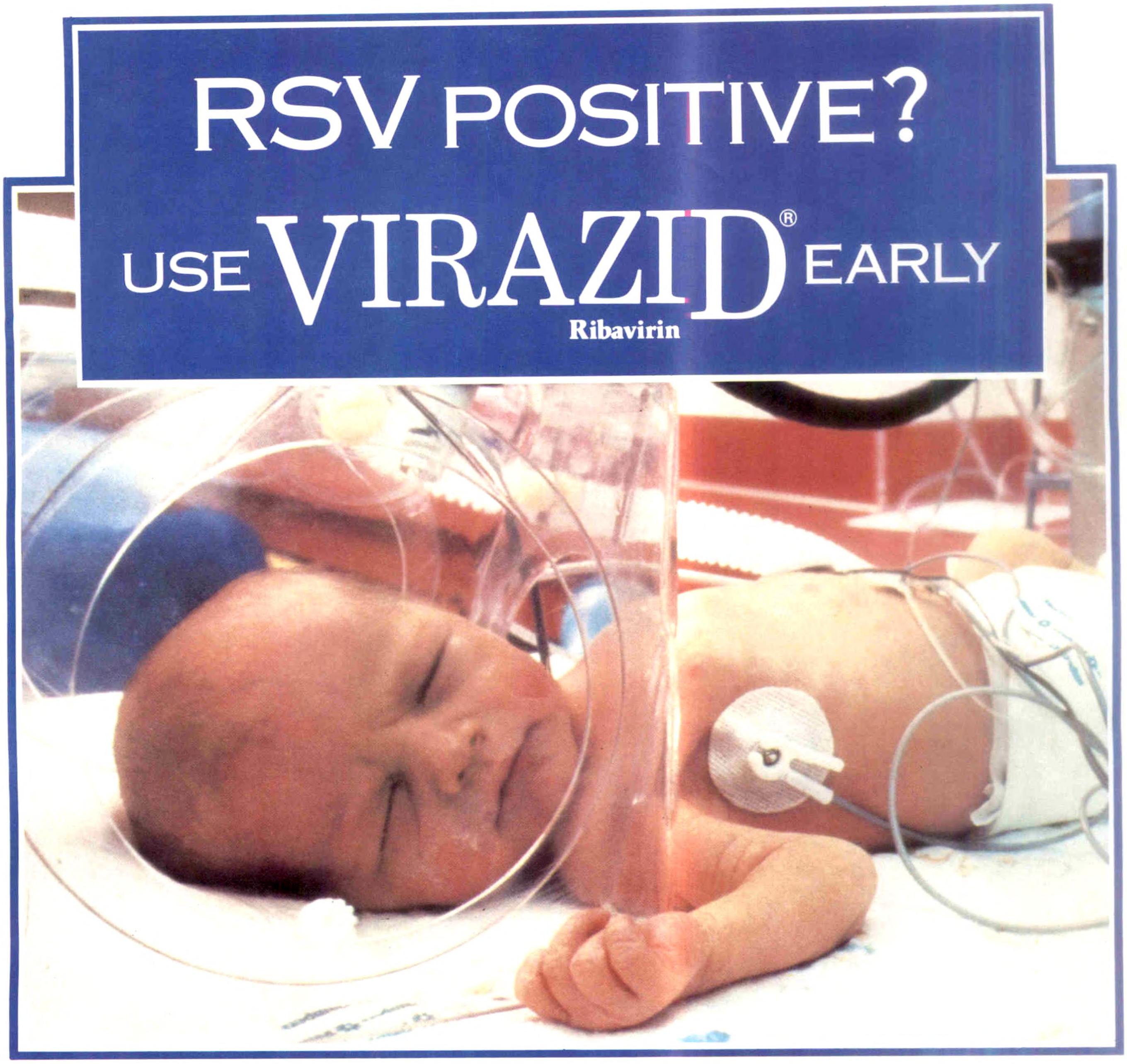
Haemorrhagic shock and encephalopathy syndrome

There seems to have been little advance in the basic understanding of this syndrome since it was first described from the Hospital for Sick Children, Great Ormond Street in 1983.[1] The clinical features have recently been redescribed in a paper from the splendidly named Children's Hospital of The King's Daughters in Norfolk, Virginia (Chaves-Carballo *et al*, *American Journal of Diseases of Children* 1990; **144**: 1079–82). They list nine diagnostic criteria: (1) age less than 10 months, (2) abrupt onset of encephalopathy, (3) fever (39°C or more), (4) shock (blood pressure less than 50 mm Hg), (5) disseminated intravascular coagulation, (6) high transaminase, (7) normal blood ammonia, (8) renal dysfunction, and, (9) exclusion of septic shock, toxic shock syndrome, Reye's syndrome, and haemolytic uraemic syndrome.

There may be a prodromal period of several days with vomiting, fever, symptoms of upper respiratory infection, or diarrhoea. The prognosis is awful. Almost all the children have either died or been left with severe neurological impairment. Corrigan in an editorial in the same issue of the journal takes up a point made repeatedly by Bacon in emphasising the importance of fever and the possible relevance of overheating in this syndrome and calls for a change of name to hyperpyrexia, shock, and encephalopathy syndrome. (Calls for a change of name, however worthy, rarely work and often confuse—unless you're a microbiologist when they both work and confuse.) Similarities between this syndrome and malignant hyperthermia lead to the thought that there could be an underlying metabolic myopathy as yet undefined. In this context it is interesting that a child in the Virginian series who was treated with a muscle relaxant had apparently less severe neurological sequelae.

We're still groping in the dark with this one. The children are desperately ill from the onset and conventional intensive care measures do nothing to lighten the gloom. First understand and then prevent seems the only approach likely to produce dividends.

ARCHIVIST



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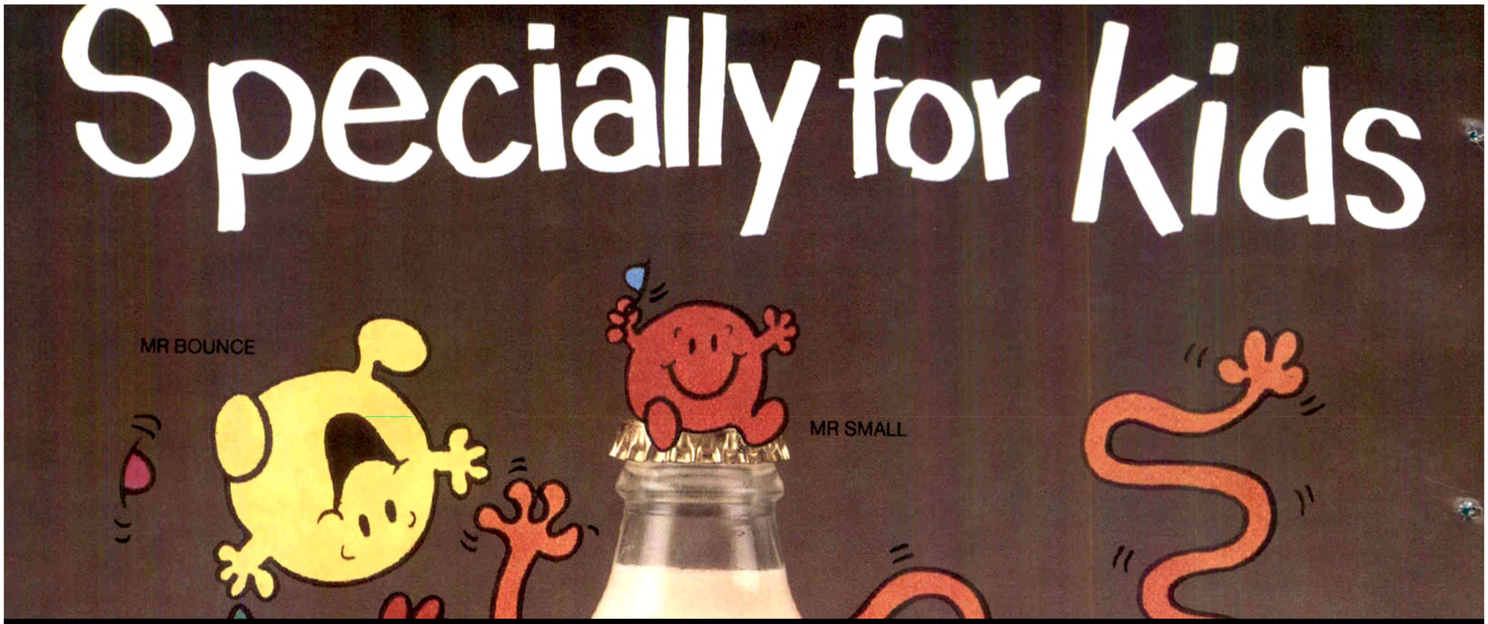

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Intractable ulcerating enterocolitis of infancy

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Abstract

Five children (three boys, two girls) presenting in the first year of life with intractable diarrhoea had a number of features in common. All had ulcerating stomatitis, four had partial villous atrophy on small intestinal biopsy, all had colitis characterised by large ulcers with overhanging edges, and four had severe perianal disease; no stool pathogens were detected. Treatment with steroids, sulphasalazine, and azathioprine was unsuccessful. All five required subtotal colectomy. Four were children of consanguinous marriages, two were siblings of Pakistani origin, two were cousins of Arab origin, and the fifth was Portuguese. Although the diagnoses of Behçet's disease and Crohn's disease were considered, it appears that these children represent a distinct inherited condition affecting the whole gastrointestinal tract, particularly the colon.

Children who have chronic diarrhoea not due to an infectious agent in the first three months of life were described as having the syndrome of intractable diarrhoea of infancy.[1] This syndrome is now defined as chronic diarrhoea in children who fail to thrive in their first year but who do not have a diagnosis that allows effective treatment.[2] It comprises a heterogeneous group of conditions, some of which have now been characterised,[3 4] but for which no cure has been found.

In many cases the cause of their clinical problem is a small intestinal enteropathy. At the Queen Elizabeth Hospital for Children, however, five such infants have presented with chronic inflammatory bowel disease, sited predominantly in the large intestine. These children also share other features and are likely to be examples of the same condition, which we have termed intractable ulcerating enterocolitis of infancy.

Two of the children have been previously reported as having an incomplete form of Behçet's disease.[5] However, their subsequent course has not shown the development of the major criteria of this condition[6] apart from aphthous stomatitis.

Patients, methods, and results

PATIENTS

The infants presented in the first two months of life (table 1), some with diarrhoea that later became bloody, and others with the passage of blood and mucus heralding the development of diarrhoea.

None of the children was of Anglo-Saxon origin. Cases 1, 2, 4, and 5 were the issue of marriages between cousins (table 1). Cases 1 and 2 were siblings and cases 4 and 5 were first cousins. Cases 4 and 5 each had two siblings who had died of intractable diarrhoea in infancy.

All five children failed to thrive, being below the third centile for weight by three months (table 2); three of the children later required parenteral nutrition.

The most striking physical signs were the development of ulceration in the mouth (fig 1) and perineal abnormalities consisting of fistulae and anal tags (fig 2). These features developed in infancy in all children except patient 3 (table 2), and occurred at around the same time as the change in bowel habit (table 1). The mouth ulcers were deep with sharply demarcated borders; they would remain for weeks before healing and then redeveloping elsewhere. The anal tags were multiple and fissures occurred spontaneously. Fistulae were seen opening onto the skin up to 3 cm from the anal margin. Genital ulcers were not observed.

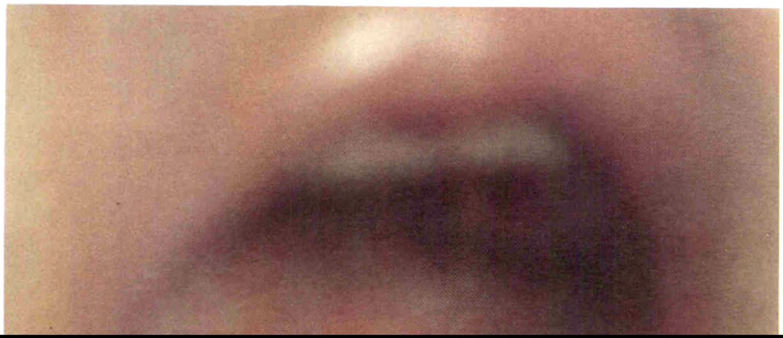
Table 2 Clinical features of children with ulcerating enterocolitis of infancy: clinical signs

Case No	*Weight centile at 3 months*	*Age of onset of mouth ulcers*	*Age of onset of perineal abnormalities*
1	<3rd	1 month	5 months
2	<3rd	1 week	3 months
3	<3rd	4 months	—
4	<3rd	5 weeks	3 months
5	<3rd	5 months	11 months

Table 1 Clinical features of children with ulcerating enterocolitis of infancy: symptoms and ethnic origin

Case No	*Presenting change in bowel habit*	*Age of change in bowel habit*	*Ethnic origin*	*Place of birth*
1*	Loose stools	5 weeks	Pakistani	England
2*	Loose stools	8 weeks	Pakistani	England
3	Blood and mucus in stools	8 days	Portuguese	Portugal
4†	Blood and mucus in stools	6 weeks	Arabic	Arabian Gulf
5†	Loose stools	6 days	Arabic	Arabian Gulf

*Siblings from consanguinous marriages.
†Cousins from consanguinous marriages.



isolated and gut autoantibodies were not present; autoantibodies to DNA, smooth muscle, gastric parietal cells, and thyroid were also negative. At first erythrocyte sedimentation rates and C reactive protein concentrations were normal, but as the illness progressed and the diarrhoea worsened with increasing amounts of blood and mucus associated with febrile episodes, these indices of inflammation became abnormal.

One notable abnormality (fig 3) was an

[redacted]

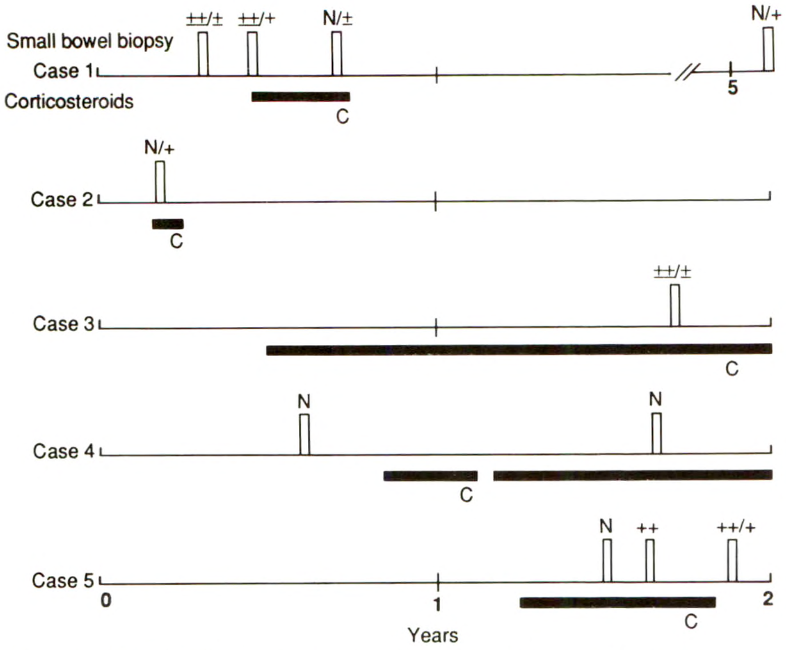


Figure 4 Small bowel biopsy appearances in five children with intractable ulcerating enterocolitis of infancy. ++=Villous height <100 μm; +=villous height 100–200 μm; N=normal small intestinal mucosa; underlining=crypt depth >200 μm; and /=patchy abnormality. The duration of prednisolone and the timing of colectomy (C) are also shown.

examination of resected specimens showed no evidence of vasculitis. In particular there was no evidence of pericapillary or perivascular localisation of monocytes; the intima was not affected and no fibrinoid necrosis was found. Granulomas were not found in the resected specimens.

In summary, abnormalities were found throughout the gastrointestinal tract (table 3). Oesophagoscopy and gastroscopy were not routinely performed in these children. It was undertaken, however, in case three who showed evidence of oesophageal ulceration, but no abnormality in the stomach or upper duodenum.

MANAGEMENT

All children had been given a diet free of cows' milk before referral. This management had not led to an alleviation of symptoms; however, cows' milk elimination was continued after referral. It was reintroduced back into the diet at the age of 2 years in cases 1 and 2.

In view of the features of chronic inflammatory bowel disease, corticosteroids were introduced (fig 4); however this treatment produced no amelioration of symptoms. Azathioprine (2 mg/kg/day) was added but despite this the children continued to have bloody diarrhoea and fevers. An eight week course of cyclosporin was given to cases 4 and 5 without improvement. An initial dose of 5 mg/kg/day was increased threefold over three weeks in order to achieve circulating concentrations of 150 μg/l. In every case the colitis became so severe that subtotal colectomy was needed to arrest deterioration.

LONG TERM SEQUELAE

After subtotal colectomy, there was a considerable improvement in the children's condition. Fevers subsided and bloody diarrhoea ceased. Ileostomy output was of good consistency despite, in most cases, evidence of a patchy

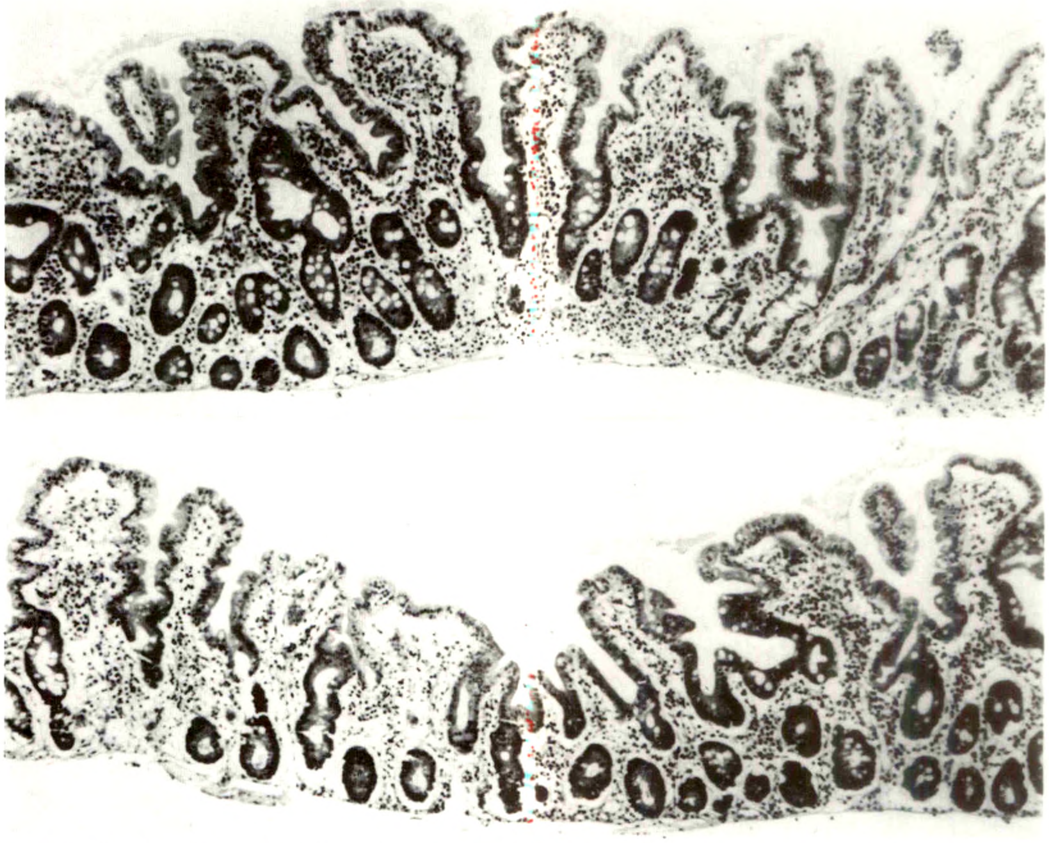


Figure 5 Histology of two sections of small intestine from a single biopsy demonstrating the patchy nature of the villous atrophy.

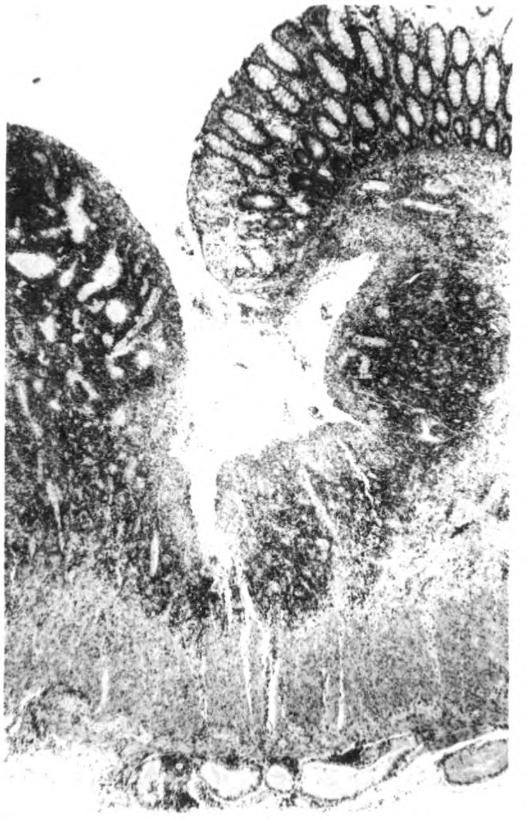


Figure 6 Histology of resected specimen of large bowel mucosa (×50) demonstrating the large flask shaped ulcer with underlying edges.

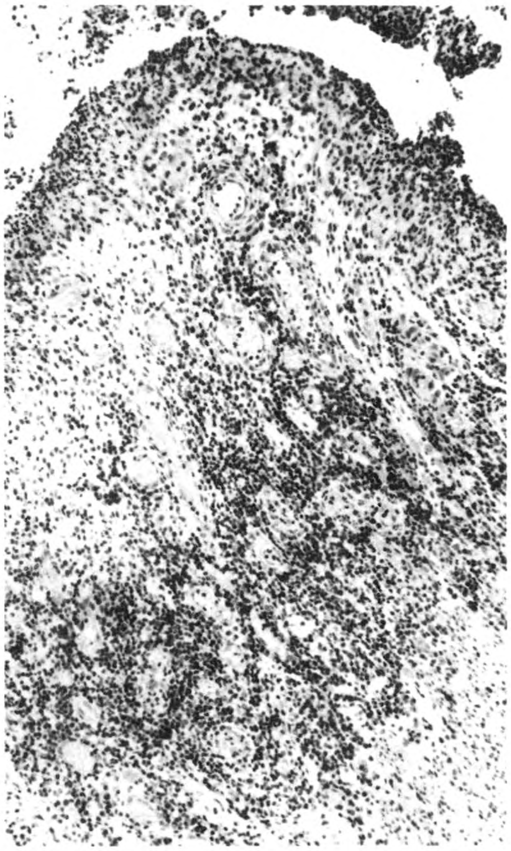


Figure 7 Histology of resected specimen of large bowel mucosa (×190) showing increased numbers of acute and chronic inflammatory cells.

Table 3 Sites of the gastrointestinal tract where inflammation was found (indicated by plus signs)

Case No	Mouth ulcers	Small bowel enteropathy	Colitis	Perineal disease
1	+	+	+	+
2	+	+	+	+
3	+	+	+	−
4	+	−	+	+
5	+	+	+	+

Table 4 Long term sequelae in patients with ulcerating enterocolitis of infancy

Case No	Time since colectomy (years)	Further problems
1	8	Anal abscess after ileorectal reanastomosis requiring further ileostomy
2	6	Fistulae around ileostomy, recurrent mouth ulcers
3	6	Ileorectal reanastomosis, recurrent ileal and rectal ulcers, mouth ulcers
4	1·5	Recurrent mouth ulcers
5	1	Ileocutaneous and jejunocutaneous fistulae, died after extensive small bowel resection

enteropathy. All children were well enough for discharge from hospital. Since then evidence of gastrointestinal inflammation has been observed in all (table 4). In one child (case 5) the inflammation extended within the small intestine to an extent where massive small bowel resection was indicated. The child later died postoperatively. In the others the inflammation, which can be particularly severe in the mouth and around the anus, has not prevented these children from living at home and leading normal life styles but has necessitated two (cases 3 and 4) to remain on low doses of systemic corticosteroids—that is less than 1 mg/kg given on alternate days. Although this treatment was ineffective in controlling the colitis, it has reduced the severity of these ulcers. The oral ulceration has affected feeding. Cases 3 and 4 are gaining weight below, albeit parallel to, the third centile, but their linear growth is now between the 25th and 50th centile. Cases 1 and 2 are thriving. Ocular inflammation or genital ulcers have never been observed.

Discussion

The similarities between these cases both clinically and pathologically make it very likely that they all have the same condition. Their abnormalities were manifest in early infancy and by 3 months of age the children were severely unwell. Each had lesions in the mouth and colon; four had small intestinal disease, and four perineal disease (table 3). None responded to immunosuppressive treatment and all required colectomy.

In the index case (case 1) the changes in the small bowel were at first thought to be a reflection of cows' milk sensitive enteropathy; but improvement was slow in response to dietary manipulation and immunosuppressive agents were used before a significant change was observed. In later cases, the enteropathies were discovered after some months of cows' milk elimination. It is probable, therefore, that the small bowel changes are part of the chronic inflammatory disease.

Alterations in the severity of patchy enteropathies are difficult to assess on repeated biopsy specimens because of sampling variation. It is possible that all children had a patchy enteropathy at the time of each biopsy, but that on some occasions only normal tissue was sampled (fig 3).

There can be no doubt that these children represent a form of chronic inflammatory bowel disease; two conditions that have some similarities are Crohn's disease and Behçet's disease.

Crohn's disease very rarely occurs in infancy. Those cases that have been reported display mainly small bowel disease with only occasional colonic involvement.[7] Some authors have cast doubts as to whether these infants did indeed have the same condition as exists in older children and adults.[8] The pathological features of the colon of the five cases presented here, who had large flask shaped ulcers and no characteristic aphthous ulcers, are not the features of Crohn's colitis and histology of the resected colons showed no granulomas.

[redacted]

when there are no features of the disease outside the gastrointestinal tract.[15] We therefore feel it unwise to label these infants as having Behçet's colitis and have described them as having intractable ulcerating enterocolitis of infancy.

A notable feature of the children is the family associations. Four of the five children are the issue of consanguinous marriages. Moreover, cases 1 and 2 are siblings and cases 4 and 5, cousins. The two pairs of siblings of cases 4 and 5 died of intractable diarrhoea of infancy and it is possible that they had a similar condition. A genetic basis for the disease is likely, possibly inherited as an autosomal recessive gene. Two familial causes of intractable diarrhoea of infancy have been described; familial enteropathy,[16] which is now thought to be the same as congenital microvillous atrophy,[3] is a defect of the enterocyte cytoskeleton and not a form of chronic inflammatory bowel disease. Secretory diarrhoea with enterocolitis cystica superficialis has characteristic dilatations of the crypts not seen in the present cases.[17]

The aetiology of intractable ulcerating enterocolitis of infancy is uncertain. All children were

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Macromolecular absorption and cows' milk allergy

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Abstract

The absorption of macromolecules was analysed by measuring serum concentrations of human α-lactalbumin after feeding human milk, using a competitive radioimmunoassay. The control group consisted of 78 children fed by cows' milk formula; concentrations of α-lactalbumin in their serum were low. The median concentrations in the different age groups varied between 7–13 μg α-lactalbumin/1 serum/1 human milk/kg body weight. Twenty eight children with cows' milk allergy were studied before introduction of a diet free of cows' milk. Nineteen had gastrointestinal and nine skin symptoms. High serum α-lactalbumin concentrations were found. Only two children had α-lactalbumin concentrations below 100 μg α-lactalbumin/l serum/l human milk/kg body weight. Altogether 76 children on a diet free of cows' milk were studied directly after a cows' milk challenge; 26 developed symptoms. They had significantly higher serum α-lactalbumin values than the 50 children with no symptoms upon challenge. Eighteen of the 26 children with symptoms had serum α-lactalbumin concentrations of more than 100 μg/l serum/l human milk/kg body weight in contrast with two of the 50 with no symptoms. Total serum IgE antibodies were analysed in 43 children. No correlation was found between concentrations of serum IgE and serum α-lactalbumin in the children with cows' milk allergy.

It is generally accepted that antigenic macromolecules can penetrate the small intestinal mucosal membranes in quantities that may be of immunological importance.[1 2] This transfer is more pronounced at an early age and even more pronounced in preterm infants.[3] It is tempting to speculate that the increased absorption of macromolecules in neonates is a natural phenomenon leading to a state of tolerance to common food antigens. Studies in animals indicate that it is easier to induce immune tolerance in younger animals given dietary antigen from birth.[4 5]

It has been reported that patients with allergic diseases have an increased permeability to macromolecules through the small intestinal mucosa.[1 6 7] It is possible that an increased absorption of macromolecules may be a part of the atopic constitution. It is also possible that an allergic reaction to food antigens may itself lead to an increased macromolecular absorption.

Methods of studying the permeability of the human intestine are based on determinations of marker molecules either in blood or urine. A number of marker proteins have been used such as bovine serum albumin, ovalbumin, cows' milk proteins, and horseradish peroxidase. Inert molecules like polyethylene glycols or polyvinyl pyrolidone have also been used as well as different carbohydrates. Synthetic polymers like polyethylene glycol molecules have a low molecular weight range from 200–2000, which is considerably smaller than most biologically important macromolecules. Besides, the transfer of these substances through the gut does not parallel the transfer of food proteins.[8]

When studying macromolecular absorption in humans with food allergy it seems most logical to use a protein molecule as a marker. When heterologous proteins, like cows' milk proteins, are used as markers local intestinal and systemic immune responses must be considered. This can be avoided by using a human protein as a marker of macromolecular absorption thereby achieving a more reliable measure of gut protein transfer.

In our studies we chose human α-lactalbumin (molecular weight 14 000), which is the dominant whey protein of human milk, as a marker of macromolecular absorption.[9]

The aim of this study was to determine whether absorption of human α-lactalbumin was increased in children with suspected cows' milk allergy, before elimination of cows' milk, and after a cows' milk challenge.

Patients and methods

A total of 78 children fed on cows' milk formula acted as controls; there were 38 girls and 40 boys. They were either healthy children at the child health unit or patients at outpatient clinics who did not have an allergy or gastrointestinal problems.

There were two groups of patients. The first group consisted of 28 children with cows' milk allergy who were studied before introduction of a cows' milk free diet (13 girls and 15 boys). The children were divided in two groups according to their symptoms. Nineteen children had gastrointestinal symptoms (diarrhoea, vomiting, abdominal pain, failure to gain weight) and nine had skin symptoms (urticaria, eczema). All became symptom free and gained weight when treated with a strict diet free of cows' milk; 15 children received soya formula (SojaSemp, Semper), and 13 casein hydrolysate formula (Nutramigen, Bristol-Myers). In all these children the symptoms vanished on a diet free of cows' milk and returned after challenge with cows' milk.

The second group consisted of 76 children

(40 girls and 36 boys) being treated with a cows' milk free diet: 44 children received SojaSemp and 32 Nutramigen. They were studied immediately after a challenge with cows' milk. The children were divided in two groups according to their symptoms. Fifty two had gastrointestinal symptoms and 24 had skin symptoms. Increasing amounts of cows' milk (1 ml–100 ml) were given during one day. Twenty six children developed symptoms on the challenge and 50 children did not.

All the children were divided into four groups according to age: 2–6 months, 6–12 months, 12–24 months, and older than 24 months.

Capillary blood samples were taken 30 and 60 minutes after intake of preheated (63°C, 30 minutes) human milk from our milk bank. Infants 2–6 months of age received 30 ml/kg body weight and infants above 6 months of age received 20 ml/kg body weight with a maximum of 200 ml.

Total serum IgE was analysed according to Kjellman *et al*[10] in 43 children and specific cows' milk IgE in serum from eight children.[10]

A competitive radioimmunoassay was used to measure concentrations of α-lactalbumin in serum.[9] No interspecies antigenic cross reactivity of human α-lactalbumin against bovine α-lactalbumin has been shown with the Ouchterlony technique, and infants fed cows' milk had no measurable amounts of human α-lactalbumin in serum.[9] Results were expressed as µg α-lactalbumin/l serum/l given human milk/kg body weight. The detection limit for the radioimmunoassay was 10 µg/l serum. Peak values (at 30 or 60 minutes) were used.

The study was approved by the ethical committee, University of Lund.

Data were analysed by the Mann-Whitney U test.

Results

The serum α-lactalbumin concentrations in the control children were low, and median concentrations in the different age groups were between 7–13 µg α-lactalbumin/l serum/l human milk/kg body weight (fig 1).

In 28 children allergic to cows' milk before the introduction of a cows' milk free diet high serum concentrations of α-lactalbumin were found (fig 2). Only two children in this group had α-lactalbumin below 100 µg/l serum/l human milk/kg body weight. The total serum IgE values were analysed in 21 children. The children with high total IgE (n=10) had a median serum α-lactalbumin concentration of 146 µg/l. The children with normal serum IgE values (n=11) had a median concentration of 150 µg/l. Cows' milk IgE antibodies were analysed in serum from three children.[10] In two of these children cows' milk IgE antibodies were found in serum. In both the serum α-lactalbumin concentrations were high (197 and 926 µg/l). The third child, however, who had no detectable cows' milk IgE antibodies, also had a high serum α-lactalbumin (625 µg/l).

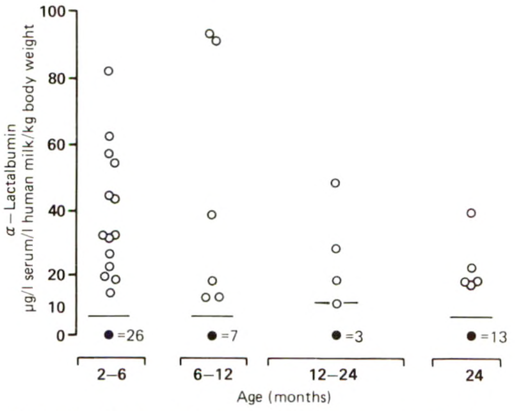

Figure 1 *Serum concentrations of human α-lactalbumin after a human milk feed in 78 control children of different ages fed on cows' milk formula. Solid circles denote children with undetectable concentrations of α-lactalbumin; the solid line shows median concentrations.*

Figure 3 shows the results from the 76 children who were studied immediately after a challenge with cows' milk. All were on a cows' milk free diet. The children who had a clinical reaction to the cows' milk challenge (n=26) had higher serum concentrations of α-lactalbumin than those who did not react to the challenge (n=50). Eighteen out of 26 children with symptoms had serum α-lactalbumin concentrations above 100 µg/l serum/l human milk/kg body

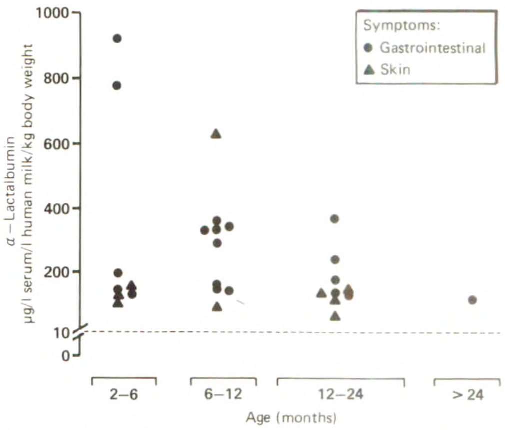

Figure 2 *Serum concentrations of human α-lactalbumin after a human milk feed in 28 children with cows' milk allergy before introduction of cows' milk free diet.*

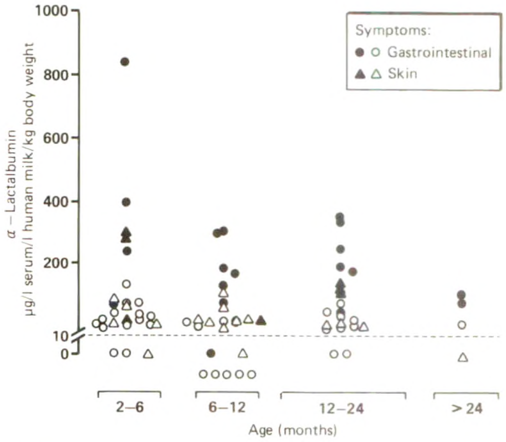

Figure 3 *Serum concentration of human α-lactalbumin after a human milk feed directly after a challenge with cows' milk in 76 children suspected of cows' milk allergy. All the children were on a cows' milk free diet. The open symbols denote the symptoms in the children who did not react to the challenge (n=50); the solid symbols denote the symptoms of those who did (n=26).*

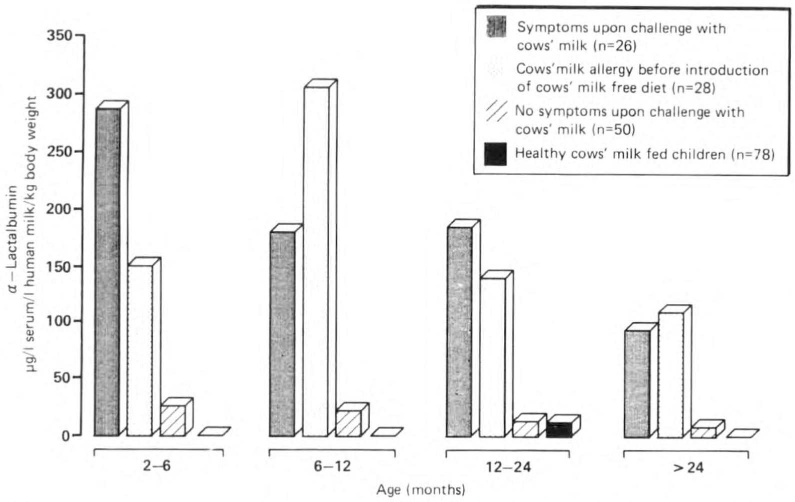

Figure 4 Serum content of human α-lactalbumin (median values) after a human milk feed in all four study groups.

weight in contrast to two out of 50 with no symptoms. One 8 month old boy who did react to the challenge had a serum α-lactalbumin concentration of <10 µg α-lactalbumin/l serum/l human milk/kg body weight. He had previously developed diarrhoea in response to cows' milk. When challenged he developed diarrhoea after the second dose of cows' milk. The diarrhoea disappeared after 12 hours. The boy was said to have cows' milk allergy but was fed with cows' milk again two weeks later without any problems.

The total serum IgE was analysed in 22 children who had a reaction on challenge. Six of these children had high total serum IgE values and a median serum α-lactalbumin of 310 µg/l. Sixteen children with normal total serum IgE values had a significantly (p=0·02) lower median serum α-lactalbumin (155 µg/l). The total serum IgE was normal in the 26 children tested who had no reaction upon challenge. Only one of eight children tested who reacted upon the challenge had measurable cows' milk serum IgE antibodies (a boy 8 months of age with a total serum IgE of 80 kU/l and a serum α-lactalbumin of 315 µg/l).

Figure 4 shows the median serum α-lactalbumin concentrations in all the groups of children. The serum α-lactalbumin in children with cows' milk allergy and children with symptoms upon cows' milk challenge are more than 10 times higher than in the control group and children with no symptoms upon challenge with cows' milk.

Discussion

This study has shown that children with cows' milk allergy, before starting treatment with a cows' milk free diet, have serum concentrations of α-lactalbumin that was more than 10 times higher than those in age matched controls. The concentrations were increased whether the children presented with intestinal or skin symptoms. The highest serum values of α-lactalbumin were found in children with gastrointestinal symptoms. Small intestinal mucosal damage caused by the allergic reaction could have been one reason for the increased absorption of α-lactalbumin.

Alternatively increased gut absorption of macromolecules may be present in all individuals predisposed to allergy. We were unable to find any correlation between serum IgE and serum α-lactalbumin concentrations in the children with cows' milk allergy. Many children with cows' milk allergy, however, do not have an IgE mediated allergy but a cell mediated immune reaction giving rise to an increase in gut intraepithelial lymphocyte counts and to various degrees of villous atrophy.[11 12]

There are, as far as we know, no earlier studies on the macromolecular absorption of homologous protein in food allgery. Results from studies using heterologous proteins are difficult to compare with ours as they are influenced by the local and systemic immunological reactions in the patients. Dannaeus *et al* studied 42 children with coeliac disease on food to determine the uptake of ovalbumin in serum after a test meal.[13] The concentrations of ovalbumin were lower in the children with high antibody values then in those with low values. The antigen concentrations were reported to be significantly lowered after treatment with sodium cromoglycate in six patients. Paganelli and coworkers demonstrated the presence of β-lactoglobulin as well as ovalbumin in a complexed form after a test meal in patients with atopic eczema as well as in normals.[14] Children allergic to cows' milk were reported to have IgA, IgG, IgE, and C_{1q} containing complexes as well as ovalbumin and β-lactoglobulin containing complexes after a cows' milk challenge, whereas healthy controls mostly had IgA and β-lactoglobulin containing complexes after a similar challenge.[15]

Our results suggesting increased absorption of protein molecules in the gut are in contrast to findings from studies using low molecular weight markers.[7 16] Du Mont *et al* studied gastrointestinal permeability in 18 atopic eczematous children compared with 10 control children using sugar mixtures of L-rhamnose and lactulose.[17] A significant difference in gastrointestinal permeability was not demonstrated between atopic and control children. Fälth-Magnusson *et al* studied gastrointestinal permeability in allergic and healthy children after treatment with sodium cromoglycate using polyethylene glycol molecules (molecular weight 400–1000).[7] There were no significant differences in the first test using polyethylene glycol between healthy and allergic children. However, after treatment with sodium cromoglycate the uptake was significantly lower in allergic children. Jackson *et al* using polyethylene glycols with higher molecular weights found that the absorption of large molecules (molecular weight 4000) was increased in all patients with eczema regardless of the presence of food allergy.[18] This was consistent with increased antigen absorption in atopic disease.

The present study has shown an increased absorption of human α-lactalbumin in children reacting to the cows' milk challenge. This could be explained in two ways: firstly, the jejunal mucosa in infants with cows' milk allergy could be damaged after exposure to cows' milk, allowing absorption of relatively large amounts of macromolecules. Secondly, an increased macromolecular absorption may be seen in these children even when free of symptoms during a cows' milk free diet.

Savilahti studied the intestinal mucosa after a milk challange.[19] He showed that at the time of clinical relapse there was a two to four times increase in the numbers of IgA and IgM containing cells in the jejunal mucosa. He suggested that cows' milk was the agent responsible for this local intestinal reaction, which coincided with the development of clinical symptoms. Further longitudinal prospective studies are needed including the repeated analyses of human α-lactalbumin absorption, to elucidate whether increased macromolecular absorption is part of an allergic constitution. Further studies are also necessary to determine whether absorption of human α-lactalbumin can be used as an objective method to measure the reaction to cows' milk after a cows' milk challenge.

In conclusion it has been found that increased absorption of proteins as measured by serum content of human α-lactalbumin occurs in children with cows' milk allergy. Whether the increased macromolecular absorption is a part of an allergic constitution or results from mucosal damage remains to be elucidated.

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Prevalence and treatment of giardiasis in chronic diarrhoea and malnutrition

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Abstract

To determine the prevalence of giardiasis in Gambian children with chronic diarrhoea and to assess their response to treatment, 31 children with chronic diarrhoea and malnutrition were investigated for giardiasis using a combination of serology (specific antigiardia IgM antibody) and microscopy of faeces and jejunal biopsy specimens. Fourteen of 31 children with chronic diarrhoea had giardiasis compared with only four of 33 healthy age and sex matched control children. Four of 15 malnourished children without diarrhoea were giardia positive. Twenty three children with chronic diarrhoea were reinvestigated after treatment with metronidazole; giardia was found in 11 of them. These results show that giardia is highly prevalent in children with chronic diarrhoea and malnutrition and that the infection does not respond to standard therapeutic measures.

Infection with *Giardia lamblia* is a recognised cause of chronic diarrhoea and malabsorption in children and may be associated with growth retardation.[1 2] High prevalence rates for giardia infection have been reported in children in developing countries even if they are asymptomatic.[1–4] Diagnosis of giardiasis is usually based on microscopic identification of either trophozoites or cysts in faeces, but this method is unreliable and may miss many cases.[5 6] Diagnostic precision can be improved by microscopic examination of duodenal aspirate,[6] endoscopic brushings,[7] or intestinal mucosa.[8] To circumvent these invasive techniques, serological methods have been developed.[9]

Giardia infection leads to a prolonged specific antigiardia IgG response that lasts for many weeks or months; it is therefore unreliable in the diagnosis of the acute infection. Specific antigiardia IgM, however, is a much better indicator of acute infection. We have developed a serum antigiardia IgM enzyme linked immunosorbent assay (ELISA) as a diagnostic test for giardiasis with a sensitivity and specificity of 96%.[9] Giardiasis can persist for many months in children who are malnourished and immunocompromised. There have, however, been no prospective studies of the impact of nutritional rehabilitation on the response to treatment of giardiasis in children with protein energy malnutrition.

The aims of this study were to find out the prevalence of giardiasis in a group of children with chronic diarrhoea and malnutrition in The Gambia, West Africa, and to assess the response to antigiardial treatment in children being treated for chronic diarrhoea and malnutrition.

Subjects and methods

The study was undertaken at the Medical Research Council's station in The Gambia, West Africa in children aged 6 to 36 months with chronic diarrhoea-malnutrition syndrome. This is defined as more than three loose stools/day persisting for more than two weeks and severe protein energy malnutrition (defined as weight for height of <75% of the National Center for Health Statistics median value). These patients (table 1) were recruited from the outpatient department and compared with age and sex matched control subjects comprising a group of well grown asymptomatic children (healthy controls) and a further group of children with protein energy malnutrition but with no history of diarrhoea (marasmic controls). Control subjects were recruited from the same geographical location as the patients with diarrhoea. While they were inpatients, all children with chronic diarrhoea malnutrition syndrome received empirical treatment with chloramphenicol 75–200 mg/kg/day and metronidazole 25 mg/kg/day for seven days.

Giardia trophozoites and cysts were sought by wet film microscopy of three consecutive fresh stool specimens (without concentration) collected before any treatment was started. There is evidence that this technique will detect giardia as reliably as concentrates.[10] In addition to standard stool microscopy, antigiardia IgM titres were determined by an ELISA and a specific antigiardia IgM antibody titre of 1:800 or more was taken to indicate active giardia infection.[9] The third diagnostic procedure in children with chronic diarrhoea malnutrition

Table 1 Demographic and nutritional data on 31 children with chronic diarrhoea and 48 controls

	Children with chronic diarrhoea (n=31)	*Healthy controls (n=33)*	*Marasmic controls (n=15)*
Mean (range) age (months)	19·0 (6–31)	16·5 (8–26)	14·2 (6–24)
Male:female ratio	15:16	20:13	8:7
Weight for height*	66·6 (50–88)	88·7 (68–104)	63·1 (46–85)
Residential area:			
Urban	11	12	3
Rural	20	21	12

*Expressed as mean (range) percentage of the National Center for Health Statistics median value.

syndrome and marasmic controls, was the identification of giardia trophozoites in sections of small bowel mucosa. Jejunal biopsy specimens were taken from the duodenojejunal junction with a modified, infant double port Crosby capsule that was introduced through the pylorus

Discussion

The results of this controlled study have shown that there is an increased prevalence of *G lamblia* infection in children with chronic diarrhoea malnutrition syndrome, and emphasise the potential importance of this organism in the

[redacted]

tion and restoration of normal immune function.

The authors thank Dr Brian M Greenwood CBE, Director of the Medical Research Council Laboratories, Fajara, The Gambia for the provision of facilities and also the medical and nursing staff of the unit for their cooperation. We give particular thanks to our field worker Miss Oumie Jabang. This project was sponsored by the Thrasher Research Fund (Salt Lake City, Utah) whose generosity and keen interest in the work are acknowledged. Dr Farthing was Wellcome Trust senior lecturer, and acknowledges the financial support of the Trust.

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The wonderful world of MRI

Just as we've got used to the beautiful anatomy textbook pictures of conventional magnetic resonance imaging (MRI) we're back in an amazing Walt Disney world with magnetic resonance angiography (MRA). Witznitzer and his colleagues in Cleveland, Ohio (*Journal of Pediatrics* 1990; **117**: 551–5) studied 10 children with sickle cell disease and cerebrovascular problems using MRI of the brain and non-invasive MRA. The moving blood gives a stronger signal and by adjusting the sensitivity the surrounding brain signals can be eliminated leaving a picture of the major vessels. For connoisseurs the name of the game is three dimensional Fourier transform time of flight MRA. Despite all that the pictures are very exciting, showing the major arteries both in the neck and inside the head and clearly demonstrating vessel occlusions. The technique will obviously be extremely useful for investigating cerebral vascular disease of all kinds in children and not only that due to sickle cell disease, and it offers a prospect of advancing our understanding of much cerebral pathology.

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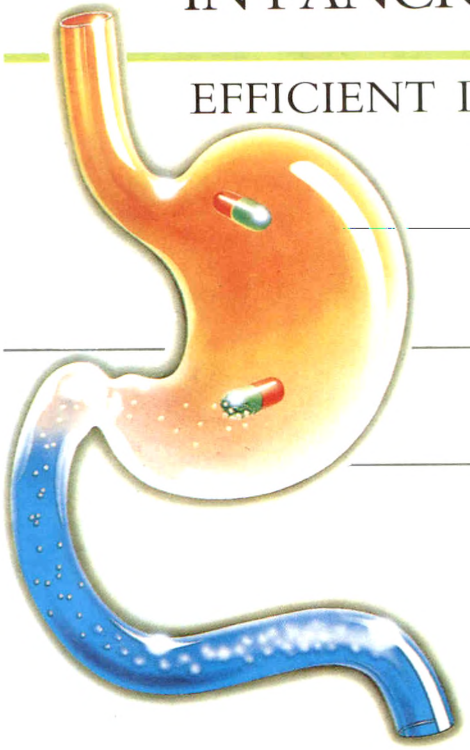

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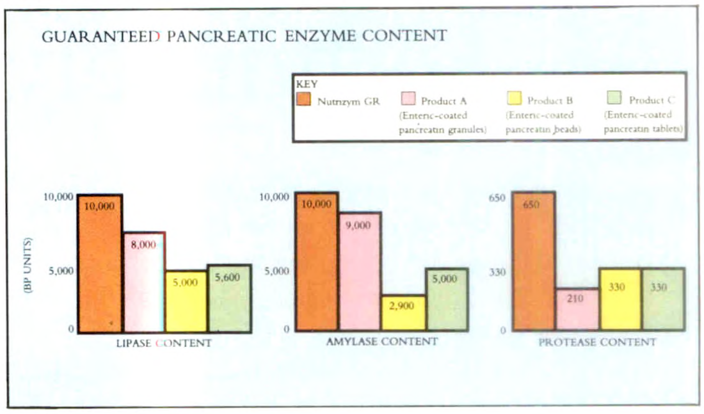

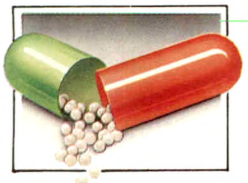

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Appendicitis in cystic fibrosis

Michael D Shields, Henry Levison, Joseph J Reisman, Peter R Durie, Gerard J Canny

[redacted]

Clinical data of the nine patients

Patient No	*Age (years)*	*Presence of meconium ileus*	*Previous DIOS*	*Duration of symptoms in days**	*Symptoms*	*Signs*	*Initial diagnosis*	*Radiological investigations*
1	14	No	No	2 (1)	Constant right iliac fossa pain, fevers and chills, nausea and anorexia, no change in stool frequency	Temperature=37·8°C, right iliac fossa tenderness, guarding and rebound, right iliac fossa mass palpable, bowel sounds normal	DIOS	Plain abdominal radiograph, contrast enema
2	6	Yes	No	1 (2)	Crampy right iliac fossa pain, no fevers, nausea, vomiting, anorexia, and constipation	Temperature=37°C, right iliac fossa tenderness and guarding, right iliac fossa mass palpable, able to walk about	DIOS	Plain abdominal radiograph
3	26	No	Yes	2 (>1)	Crampy right iliac fossa pain, nausea and vomiting, no fevers, no change in stool frequency	Temperature=37·8°C, right iliac fossa tenderness and guarding, right iliac fossa mass palpable	Appendicitis	Plain abdominal radiograph
4	17	Yes	No	1 (<1)	Crampy right iliac fossa pain, constipation, fevers	Temperature=38·5°C, right iliac fossa tenderness, guarding, and rebound, absent bowel sounds, no mass	Appendicitis	—
5	14	No	No	2 (<1)	Right iliac fossa pain, diarrhoea, fever	Temperature=37·3°C, right iliac fossa tenderness and rebound: no mass, bowel sounds normal	Appendicitis	—
6	23	No	Yes	2 (3)	Constant right iliac fossa pain, fevers and chills, nausea, vomiting, anorexia, and constipation	Temperature=39·0°C, right iliac fossa tenderness, guarding, and rebound, right iliac fossa mass palpable, able to walk about	DIOS	Plain abdominal radiograph, contrast enema, abdominal ultrasound scan
7	4·5	Yes	Yes	22 (3)	Crampy right iliac fossa pain, no fever, nausea, anorexia, and constipation	Temperature=36·0°C, right iliac fossa tenderness, masses palpable in both right iliac fossa and left lower quadrant of abdomen, able to walk about	DIOS	Plain abdominal radiograph, contrast enema, abdominal ultrasound scan
8	13	Yes	No	5 (40)	Right hip pain, unable to walk, no fevers, no nausea, haematemesis from varices	Temperature=37·0°C, no abdominal pain, right hip flexed and abducted	Psoas abscess	Plain abdominal radiograph, contrast enema, abdominal ultrasound scan, abdominal computed tomogram
9	35	No	Yes	9 (47)	Constant right iliac fossa and suprapubic pain with dysuria, fevers and chills, no change in stool frequency	Intermittent fevers up to 39·0°C, right iliac fossa tenderness, guarding, and rebound, right iliac fossa mass palpable, able to walk	DIOS	Plain abdominal radiograph, contrast enema, abdominal ultrasound scan, abdominal computed tomogram, gallium scan

*Symptom duration before presentation to hospital (time interval between hospital admission and time of surgery).
DIOS=distal intestinal obstruction syndrome.

Plain abdominal radiographs were performed in seven patients and in four patients faecal impaction of the colon and caecum was evident. Three patients had small bowel air-fluid levels and in one of these the small bowel was minimally dilated. The abdominal radiograph of the patient thought to have a psoas abscess showed a prominent psoas shadow and a few air-fluid levels in the small bowel near to the caecum.

Contrast enemas were performed in all of the patients with a delayed diagnosis and in one other patient. In three of these, the caecum was noted to be loaded with faeces, and in one patient the caecum was also indented by an extrinsic mass. Indentation of the caecum, without faecal impaction, was noted in another case, and the remaining study showed an irregularity of the caecum. In no case was filling of the appendix with contrast demonstrated.

Ultrasound scans of the abdomen were performed in the four patients with delayed diagnosis. Two of these scans were reported as normal, and one scan showed a mass in the right iliac fossa that was thought to be faeces, although a periappendicular mass could not be excluded. The ultrasound scan of the patient presenting with limited hip movement showed an enlarged right psoas muscle with surrounding fluid extending to the caecal region, and was interpreted as a primary psoas abscess. An abdominal computed tomogram was performed on two patients: that of patient 8 was also consistent with a psoas abscess, and the other was performed in patient 9 and was reported as normal. This patient also had two gallium scans of the abdomen, the first was normal, and the repeat showed diffuse radionuclide uptake in the lower abdomen and pelvis.

SURGICAL FINDINGS

The decision to perform an appendicectomy in patients 1–5, was based on clinical deterioration and the development of the classical features of appendicitis with peritoneal irritation. With respect to the four patients with delayed diagnosis, a laparotomy was performed in two of these patients when they failed to respond to medical treatment for DIOS and fever, toxicity, and peritoneal irritation developed. Although the results of ultrasound and computed tomography in patient 9 were normal, he eventually underwent a laparotomy because of persistent fever and pain in his right iliac fossa with a palpable mass. Although the patient with a suspected psoas abscess had a partial response to intravenous antibiotics, a repeat contrast enema revealed an inflamed and fibrosed small bowel proximal to the caecum (possibly representing the appendix), and a repeat computed tomogram showed a residual abscess in the psoas region. He underwent an interval appendicectomy two months later.

All but one (patient 5) of the children had periappendicular abscesses identified at surgery. In addition, one patient had a perforated appendiceal diverticulum. Bacterial cultures from the abscess fluid were available in five patients and the following organisms were grown: *Escherichia coli* (n=2), *P aeruginosa* (n=1), bacteroides (n=1), and no growth in one case. All of the patients survived surgery.

Discussion

Despite the fact that the appendix in patients with cystic fibrosis is frequently swollen and distended with inspissated eosinophilic secretions, it is ironic that the reported incidence of acute appendicitis in these patients is lower than that in the general population.[3–8] During the past 10 years, only nine of 803 (1·1%) patients attending this cystic fibrosis clinic have developed appendicitis. Likewise, McCarthy *et al* reported an incidence rate for appendicitis among patients with cystic fibrosis of 1–2% compared with a 7% rate in the general population.[4] These authors suggested that the low incidence of appendicitis among patients with cystic fibrosis may be related to a protective effect of mucous secretions within the appendix, which maintain the appendiceal lumen distended and less prone to total luminal occlusion and acute inflammation. It is also possible that the long term use of oral antibiotics for pulmonary prophylaxis accounts for the low incidence of appendicitis in cystic fibrosis and masks the symptoms of appendicitis.[4 5]

Our report highlights the difficulty with which the diagnosis of appendicitis is made in patients with cystic fibrosis, and this has also been the experience of others.[2–6] Several factors account for the delay in diagnosis in our patient group. In general, the history and physical findings of our patients on presentation were less 'dramatic' and impressive than seen in patients without cystic fibrosis who develop acute appendicitis, and this may in part have been related to long term antibiotic use.[4 5] In one patient the diagnosis was overlooked initially because of a very atypical presentation and radiological findings suggestive of a primary psoas abscess. In our experience, however, the main reason for the delay in the diagnosis of appendicitis was that five of our patients were initially considered as having DIOS, which occurs in 4% of our clinic population.[1] The presenting history and physical findings (particularly that of a mass in the right iliac fossa) certainly made the diagnosis of DIOS a distinct possibility in these patients, and in addition, all of the patients were pancreatic insufficient and four had a history of DIOS. The picture was confused further by the finding of faecal impaction of the caecum on plain abdominal radiographs and ultrasound scans in some of our patients, again consistent with the diagnosis of DIOS.[1]

As a result of the delay in reaching the correct diagnosis, appendiceal perforation and abscess formation was found in all but one of our patients at the time of surgery. Interestingly, three of the four patients described by Jaffe *et al*,[3] and all of the 10 patients reported by Dalzell *et al*,[2] McCarthy *et al*,[4] and Holsclaw and Habboushe,[5] were also found to have periappendiceal abscesses at surgery. Appendiceal perforation was noted in 13 of 34 patients described recently by Coughlin *et al*.[6] One of our patients was noted to have an appendiceal diverticulum, a lesion which is considered to be more common in patients with cystic fibrosis.[14]

A variety of modern radiographic techniques have been recommended in order to differentiate the common causes of abdominal symptoms with a right iliac fossa mass in cystic fibrosis patients—that is, DIOS, intussusception, faecalith, and appendiceal abscess.[4 11 12] In our series four patients had ultrasound examinations, two had computed tomograms, and one had a gallium scan, none of which was helpful in reaching a diagnosis of periappendiceal abscess. Contrast enemas were performed in five of our patients for diagnostic as well as therapeutic (for DIOS) reasons. The contrast studies were helpful in the sense that they did rule out the possibility of intussusception. In three of these five studies, however, faecal impaction of the caecum was found that led initially to the mistaken diagnosis of DIOS (in one of these studies caecal indentation by an extrinsic mass was also noted). The other two patients who underwent contrast enemas were found to have an extrinsic indentation of the caecum and a caecal irregularity respectively. The patient with the extrinsic compression of the caecum was initially thought to have a primary psoas abscess, a suspicion which was further supported by an abdominal ultrasound scan and computed tomography. The patient with caecal irregularity on contrast enema had normal results on computed tomography, ultrasound and gallium scans of the abdomen (patient 9). This patient experienced the longest delay before a diagnosis of appendiceal abscess was reached at laparotomy, which was performed in view of persistent symptoms and diffuse uptake of gallium over the lower abdomen on a repeat scan.

In summary, the diagnosis of appendicitis and its complications is difficult in patients with cystic fibrosis, despite the availability of modern radiographic techniques. Although DIOS remains the most common cause of abdominal pain and a mass in the right iliac fossa in cystic fibrosis patients, our cases indicate that an appendix abscess may mimic this condition. This diagnosis should be considered particularly in patients who fail to respond to medical treatment for DIOS, and who are found to have an extrinsic caecal compression on contrast enema.

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On the trail of the Lone Star tick

The Lone Star tick (*Amblyomma americanum*) lives in the south and east of the United States and is most likely to bite you in spring and early summer. It is known to be a vector, though not the most common one, of Rocky Mountain spotted fever but is now suspected of harbouring a newly described rickettsial disease, ehrlichiosis. The diagnosis can be confirmed serologically in fewer than a quarter of people suspected of having Rocky Mountain spotted fever. The differential diagnosis of fever after tick bite includes tularaemia, Lyme disease, babesiosis, and now ehrlichiosis.[1] A recent paper in the *Journal of the American Medical Association* (Eng *et al*, *JAMA* 1990; **264**: 2251–8) gives details of the clinical and laboratory findings in this disease which is thought to be caused by the rickettsia *Ehrlichia canis,* though the organism has not been isolated from patients and the diagnosis depends on demonstrating a fourfold rise in antibody titre in paired sera. Samples sent to laboratories throughout the United States for testing for Rocky Mountain spotted fever were also tested for ehrlichiosis and 40 of 541 paired samples proved positive. Seven were from children.

The disease follows the tick bite by about seven days on average (range 1–21 days) and is characterised by prolonged fever with recovery after about three weeks in children, who generally have a less severe illness than adults. All children, but only a third of adults, develop a rash on the trunk and/or extremities that is either maculopapular or petechial. Diarrhoea and pulmonary infiltrates on *x* ray each occurred in about three quarters of the children and hepatosplenomegaly in a third. Lymphadenopathy, anaemia, leukopenia, and thrombocytopenia were common as was a raised serum transaminase. Treatment with either a tetracycline or chloramphenicol was effective but cephalosporins, penicillins, erythromycin, or co-trimoxazole not so.

These diseases have a fascination of their own, but it is said that the United States is about to take over from Spain the sometimes dubious privilege of being the most favoured destination of British holidaymakers. As many of those may head for the south eastern corner of the country it is not impossible that the trail of at least one Lone Star tick might end on a British children's ward.

ARCHIVIST

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Effect on intelligence of relaxing the low phenylalanine diet in phenylketonuria

Isabel Smith, Martin G Beasley, Anthony E Ades

Abstract

ated with a further decline in intelligence or in

[redacted]

was small (1 IQ point in cohort I and 0·4 points in cohort II) and does not affect the interpretation of the association between the phenylalanine control and IQ.

PSYCHOLOGICAL ASSESSMENTS

IQs were measured at the age of 4 years using the Stanford-Binet (short form L-M, 1960 revision) and at 8 years using the full forms of either the Wechsler intelligence scale for children (WISC) (cohort I), or revised WISC (WISC-R) (cohort II). IQs were remeasured at 10, 12, and 14 years of age using the same procedures as at 8 years.

As discussed previously,[1] in the United States and Europe, including the United Kingdom, a steady rise in population IQ scores (of approximately 0·3 points per year from the time of standardisation onwards) has been occurring for all commonly used test procedures. A method of converting IQs to standard deviation scores (IQ-SDS), which allows for the influence of population trends and the differences between tests, has been described and is used again here.[1] As the present study was concerned with longitudinal IQ trends in the same children (rather than in succeeding generations of children) population norms have been based on the year of the first assessment at 4 years of age—that is: revised Stanford-Binet norms=98+0·3 (birth year+4−1932); revised WISC norms=100+0·3 (birth year+4−1947·5); and revised WISC-R norms=102·6+0·3 (birth year+4−1972). IQ-SDS was then calculated by subtracting the estimates of the population IQ norms from the actual IQs, and dividing by the standard deviation for the test procedure concerned (Stanford-Binet 16, WISC 15, WISC-R 14).

TYPE OF PHENYLKETONURIA

The register classifies subjects as 'atypical', 'possibly atypical', or 'classical' according to peak phenylalanine concentrations during a period of relaxation in the dietary restrictions after the first birthday (<900 μmol/l, 900–1200 μmol/l, and >1200 μmol/l respectively). As so few treated subjects fell into the 'atypical' category (seven in cohort I, 20 in cohort II) for the purposes of the present study they were merged with the 'possibly atypical' group to form a single, 'non-classical' group (25 (11%) in cohort I, 87 (23%) in cohort II).

DIETARY CONTROL OF PHENYLALANINE CONCENTRATIONS

Dietary treatment was classified at each birthday according to the total recorded phenylalanine intake (strict=<500 mg/day or less, relaxed=500 −1000 mg/day), free=>1000 mg/day). Stopping treatment was defined separately as the age at which the regular intake of a phenylalanine-low protein substitute ceased. Phenylalanine concentrations were categorised and plotted against time in order to estimate area under the curve, as described previously.[1 2] Because phenylalanine values were usually measured using semiquantitative methods (which become progressively less accurate as phenylalanine concentrations rise above 1200 μmol/l) all values >1200 μmol/l were coded into a single category. Relatively few quantitative results recorded up to 14 years were above 1500 μmol/l and phenylalanine values in the top category were set at 1350 μmol/l (the mid-point between 1200 and 1500 μmol/l) for the purposes of calculating average phenylalanine values. Means were calculated for each year of life and for eight composite follow up periods: birth –4, 5–8, 9–10, 9–12, 11–12, 11–14, 13–14 years.

STATISTICAL METHODS

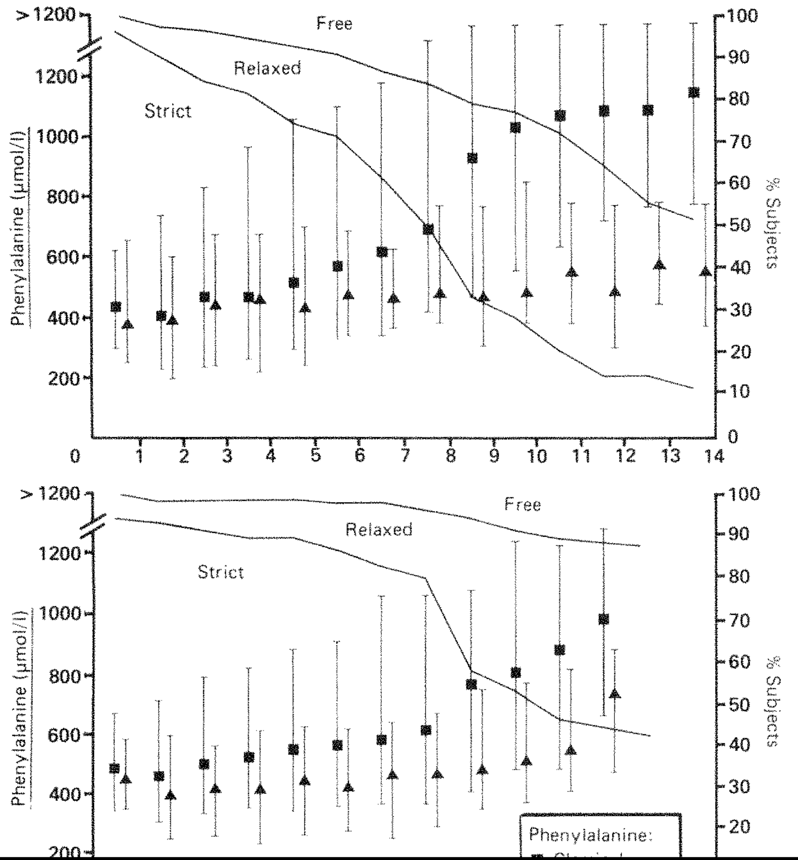
Trends in phenylalanine control, dietary intake, and IQ-SDS were examined in relation to age. The associations between IQ-SDS and dietary control at different ages were examined in a series of tables. Multiple regression was used to determine whether IQ at different ages was related to blood phenylalanine concentrations during the periods between assessments, controlling both for IQ at the beginning of the periods and the history of phenylalanine control. Also included in the regressions were social class and type of phenylketonuria (as class variables) and four factors (as continuous variables) relating to diagnosis and early management that had previously been shown to relate to IQ-SDS at 4 years (diagnostic phenylalanine concentrations, age at start of treatment, duration of phenylalanine concentrations below 120 μmol/l in first two years and birth year).[1]

Results

TRENDS IN DIETARY CONTROL AND IQ-SDS WITH AGE

Figure 1 summarises overall dietary trends from the start of treatment to the 14th birthday in cohorts I and II respectively. The figures show the annual percentages of children receiving a strict, relaxed, or free diet at each birthday and median blood phenylalanine concentrations (with 10th and 90th centiles) in classical and non-classical subjects separately. In cohort I dietary follow up was complete but in cohort II the trends are based on declining numbers (375 up to 8 years to 130 at 12 years) because only a minority of subjects had reached their 14th birthday. After 12 years there were too few subjects for analysis.

The proportion of subjects receiving a strict diet fell with increasing age. The fall was steeper in cohort I in which less than 50% of subjects were receiving a strict diet at the age of 8 years and only 11% at 12 years. In cohort II 80% were still receiving a strict diet at 8 years and 40% at 12 years. Up to 4 years of age the median phenylalanine values were relatively stable at around 400–450 μmol/l although in cohort II, even before 4 years, median values tended to be higher in classical compared with non-classical subjects. After 4 years classical subjects in both cohorts showed a steady rise in median phenylalanine values in parallel with the relaxation of the diet; the rise was steeper in cohort I than cohort II. Non-classical subjects



lower than expected in the general population and standard deviations centred around 1. Subjects in cohort I and those with classical phenylketonuria did worse than those in cohort II and with the classical disorder.

ASSOCIATION BETWEEN IQ-SDS AND PHENYLALANINE CONTROL

In both cohorts and at all ages, mean IQ-SDS fell as average phenylalanine concentrations in the period preceding assessment rose. As non-classical subjects tended to have higher mean IQ-SDSs and also had better phenylalanine control than subjects with the classical disorder, the association between IQ-SDS and phenylalanine control was re-examined in classical subjects alone; the data for 8 years of age is shown in table 1. An inverse trend between IQ-SDS and average phenylalanine concentrations between 5 and 8 years persisted. IQ-SDS was also inversely related to earlier age at which the annual phenylalanine average concentration reached 900 μmol/l and children who stopped their protein substitute before 8 years did worse than the others. There were too few non-classical subjects to permit meaningful tabulation in the same way.

As mean phenylalanine concentrations after 4 years were closely correlated with phenylala-

[redacted]

Table 1 Association between IQ-SDS at 8 years of age and dietary control (classical subjects only)

	Cohort I		Cohort II	
	No (%)	Mean IQ-SDS	No (%)	Mean IQ-SDS
Mean phenylalanine from 5–8 years (μmol/l)				
<400	27 (14)	−0·54	42 (15)	−0·14
401–500	41 (21)	−0·24	65 (23)	−0·38
501–600	34 (17)	−0·61	52 (18)	−0·47
601–700	29 (15)	−0·61	45 (16)	−0·95
701–900	28 (14)	−1·10	50 (17)	−1·14
>900	39 (19)	−1·96	33 (11)	−1·48
Age annual phenylalanine became >900 μmol/l (years)				
>8	124 (62)	−0·47	204 (70)	−0·45
7–8	26 (13)	−1·16	35 (12)	−0·83
5–6	16 (8)	−1·62	19 (7)	−1·39
3–4	23 (12)	−1·81	19 (7)	−1·73
1–2	10 (5)	−1·47	11 (4)	−2·03
Age diet stopped*				
>8 years	157 (79)	−0·70	272 (94)	−0·64
1–8	42 (21)	−1·45	16 (6)	−1·76
All subjects	199 (100)	−0·86	288 (100)	−0·71

*Age at which administration of phenylalanine-low protein substitute ceased. The number of subjects who stopped before the 8th year was too small to allow for meaningful subdivision.

Table 2 Association of IQ-SDS at 8 years of age and change in IQ-SDS between 4 and 8 years to mean phenylalanine concentration in μmol/l from birth to 4 years and 5 to 8 years

	Phenylalanine 0–4 years	Phenylalanine							
		Cohort I				Cohort II			
		≤600 No	IQ-SDS	>600 No	IQ-SDS	≤600 No	IQ-SDS	>600 No	IQ-SDS
IQ-SDS at 8 years	<600	120	−0·38	58	−1·12	227	−0·24	88	−0·99
	>600	3	−0·01	42	−1·49	10	−1·04	48	−1·37
Change in IQ-SDS 4–8 years	<600	120	+0·23	58	−0·06	227	+0·02	88	−0·30
	>600	3	+0·04	42	−0·13	10	−0·28	48	−0·23

Table 3 Summary of regression analyses. IQ-SDS as dependent variables with estimates (SE) of slopes of regression lines relating IQ-SDS to a 1000 μmol/l change in mean phenylalanine concentrations in period immediately before assessment

Outcome variable IQ-SDS (years)	Regressor variable phenylalanine (years)	Cohort I			Cohort		
		No	Estimates (SE)*	p Value	No	Estimates (SE)*	p Value
4	0–4	191	−1·72 (0·43)	<0·0001	316	−2·10 (0·41)	<0·0001
8	5–8	191	−1·42 (0·32)	<0·0001	316	−0·88 (0·29)	0·001
10	9–10	168	+0·15 (0·22)	NS	186	−0·52 (0·20)	0·02
12	9–12†	167	+0·28 (0·25)	NS	86	−0·58 (0·38)	NS
14	11–14†	159	+0·01 (0·27)	NS		Not done	

*Estimates adjusted for social class, type of phenylketonuria, IQ-SDS at previous follow up (except at 4 years), phenylalanine concentrations before 4 years, and four variables relating to diagnosis and early management (see methods).
†Similar results were obtained for periods 11–12 and 13–14 years.

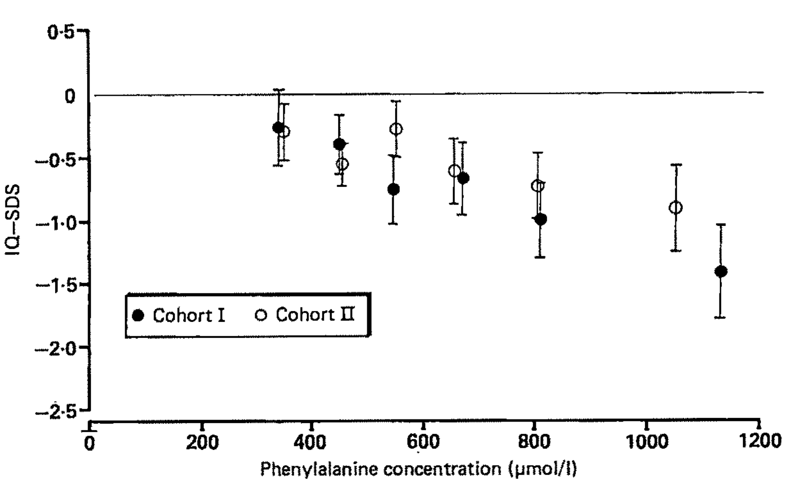


Figure 3 Association between IQ-SDS at 8 years and mean phenylalanine concentrations between 5 and 8 years after allowing for the influence of IQ-SDS at 4 years, mean phenylalanine between birth and 4 years, social class, type of phenylketonuria, and four factors related to diagnosis and early management (see methods) using regression analysis.

ciation more fully. Social class, type of phenylketonuria, and the four factors relating to diagnosis and early management (see methods) were included in the regression equations, along with IQ-SDS at 4 years, average phenylalanine concentrations in the period 0–4 years as a continuous variable, and average phenylalanine concentrations 5–8 years as a class variable.

In both cohorts IQ-SDS at 8 years was highly and directly correlated with IQ-SDS at 4 years (cohort I $F_{1,175}=96{\cdot}9$, $p>0{\cdot}0001$, cohort II $F_{1,301}=140{\cdot}0$, $p<0{\cdot}0001$). However, even after allowing for IQ-SDS at 4 years and all other factors, IQ-SDS at 8 years was independently and inversely associated with average phenylalanine control between 5 and 8 years (cohort I $F_{5,175}=4{\cdot}5$, $p<0{\cdot}0007$, cohort II $F_{5,301}=2{\cdot}8$, $p<0{\cdot}016$). The means for IQ-SDS at 8, adjusted for the effects of the other covariates by regression, are plotted against mean phenylalanine in fig 3.

The trends were similar in both cohorts and linear. With the exceptions of a positive association with birth year in cohort I ($F_{1,175}$=5·9, p=0·016) and a negative association with phenylalanine control 0–4 years in cohort II ($F_{1,301}$=6·0, p=0·015) there were no further independent associations between IQ-SDS at 8 years and any other variables. Type of phenylketonuria had no independent influence on IQ-SDS once allowance was made for phenylalanine control.

Similar regression analyses were carried out to examine the association of IQ-SDS at ages 8, 10, 12, and 14 years to mean phenylalanine concentrations in the period between assessments, now treated as a continuous linear variable, while controlling for the other factors. Thus at age 10 years IQ-SDS was regressed against average phenylalanine concentrations between ages 9–10, while controlling for: IQ-SDS at 8, phenylalanine concentrations between birth and 4 years and between 5 and 8 years, social class, type of phenylketonuria, and the four factors relating to diagnosis and early management. At 12 years phenylalanine control between 11 and 12 years was added to the equation and at 14 years IQ-SDS at 8 years was replaced by IQ-SDS at 10 years and phenylalanine control 13–14 years was added. An analysis of IQ-SDS at 4 years in the children also tested at 8 years was included for comparison, although no preceding IQ-SDS was available for inclusion in the analysis.

Estimates of the slopes of the regression lines at different ages are set out in table 3; these represent the effect on IQ-SDS of an 1000 µmol/l rise in phenylalanine. The results at 4 years were similar in both cohorts. At 8 years the slopes of the regression lines were somewhat less than at 4 years, particularly in cohort II, but were still significant. In cohort I after 8 years of age the association between IQ-SDS and mean phenylalanine control was no longer evident, though, in cohort II, a significant negative association between IQ-SDS and phenylalanine control persisted (though with a lower slope) and was still significant at 10 years.

From the slopes shown in table 3 it is predicted that for each 300 µmol/l rise in mean phenylalanine concentrations in the first 4 years of life, IQ at 4 years fell by 7 points in cohort I and 10 points in cohort II. After allowing for events up to 4 years, a rise of 300 µmol/l in mean phenylalanine concentrations between 5 and 8 years was associated with a fall in IQ at 8 years of 6 points in cohort I and 4 points in cohort II. At 10 years IQ in cohort II fell 2 points for the same rise in phenylalanine. Similar results were obtained in regression models which examined each two year interval after 10 years, and also models which did not include adjustments for the variables related to events up to four years and phenylalanine concentrations before the preceding IQ.

Discussion

We have reported previously that intelligence at 4 years of age in children with phenylketonuria in the United Kingdom who were treated early was lower than expected in the general population, probably due to some degree of neurological impairment occurring despite dietary treatment, and that intelligence was inversely and linearly associated with average phenylalanine control from birth to 4 years.[1]* The present study shows that, even after taking events up to 4 years into account, intelligence at 8 years was still inversely associated with phenylalanine control between 5 and 8 years. A tendency for IQ to rise between 4 and 8 years in subjects with good control and to fall in those with poor control accounted for the lack of change in the mean IQ between the two ages.

After 8 years, despite a steep rise in blood phenylalanine concentrations, the association between intelligence and phenylalanine control was no longer evident in children born earlier. However, in those born later an inverse association between intelligence and phenylalanine control persisted to at least 10 years, although the association was less noticeable than at earlier ages. Later born subjects also differed from the earlier born in having higher IQs at all ages although, as discussed previously,[1] our analysis does not fully explain this difference.

An explanation for the association we have documented between intelligence and phenylalanine control up to 8–10 years is that raised brain phenylalanine concentrations, via closely related biochemical events such as deficiency of neuronal amino acids[9] and increased myelin turnover,[10] exert an adverse, dose related effect on brain growth and development, greatest during early childhood and declining gradually thereafter. This interpretation is consistent with what is known about the natural history of the untreated condition[7] and with previous reports that children deliberately placed on a normal diet at or before 8 years showed falls in IQ[3 4] or in educational progress[5] after the change in treatment. Our findings are also in agreement with those of the American Collaborative Study, which showed that lower IQ was associated with earlier age (up to 8 years) at which average phenylalanine concentrations reached 900 µmol/l.[6]

Nevertheless, an indirect contribution to the association between intelligence and hyperphenylalaninaemia cannot be ruled out. In our study the minority of subjects with non-classical phenylketonuria (defined as failure of blood phenylalanine concentrations to rise above 1200 µmol/l during a period of dietary relaxation) did consistently better than those with the classical disorder with respect to both intelligence and phenylalanine control. This intellectual advantage in non-classical subjects could be fully accounted for by their better phenylalanine control. As a child grows older and dietary treatment is less strictly maintained, however, there is wider variation between patients in phenylalanine concentrations. It is possible that this increased variation provides an additional and more sensitive index of 'severity' than the other

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[*] In our previous paper a lower figure was given of 'approximately 4 points for each 300 µmol/l rise in mean phenylalanine concentrations'; this was an error and should have read 'approximately 8 points for each 300 µmol/l rise in mean phenylalanine concentrations'.

variables we have used and might, therefore, be an additional determinant of the adverse effects of phenylketonuria on the nervous system, associted with but not wholly dependent on phenylalanine control. Nevertheless, that the associations between intelligence and phenylalanine control after 4 years persisted after controlling for IQ at 4 years and the history of phenylalanine control, provides strong support for the view that phenylalanine excess exerts a direct and dose dependent effect on intellectual progress.

Whatever the correct explanation for associations between intelligence and dietary control at different ages, the results suggest a decline in the size of the association as children become older and particularly after 8 years, despite their much higher phenylalanine concentrations. This probably indicates that, by mid-childhood, maturation of the nervous system has advanced to a stage where the parameters of 'intelligence' have stabilised and are therefore less vulnerable to the biochemical effects of phenylketonuria.

The relatively stable intellectual state in older children does not preclude the development of other manifestations of neurological impairment. Four early treated subjects (0·4% of register subjects aged over 12 years) are known to have developed new and major neurological problems (paraplegia and epilepsy) in adolescence or early adult life and lesions in the subcortical white matter were found on magnetic resonance imaging.[11] The literature contains several other case reports of new neurological abnormalities developing in both late and early treated adolescents and young adults with phenylketonuria.[7 12 13] In addition postmortem studies have documented signs of active demyelination[12 14] as well as hypomyelination and reduced brain size. White matter changes on magnetic resonance imaging have also been reported in children without neurological deterioration but with a history of poor phenylalanine control.[15]

We conclude that optimal intelligence is unlikely to be achieved in children with phenylketonuria unless phenylalanine concentrations are mostly below 400 μmol/l throughout the first half of childhood. In children with severe classical phenylketonuria it is difficult to maintain phenylalanine concentrations within a very narrow range and such children are likely to be at a particular risk of intellectual impairment. Even though the changes of intellectual deterioration due to high phenylalanine concentrations appear to diminish as the child grows older, in some individuals at least, phenylketonuria poses a lifelong hazard to the integrity of the nervous system. Patients with phenylketonuria will, therefore, have to be advised to continue a low phenylalanine diet indefinitely, despite the uncertainties and real practical difficulties involved. As subjects pass through adolescence and early adult life it will be important to continue monitoring progress so that more information can be obtained concerning the size of risk to the nervous system and the factors related to neurological deterioration.

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Leukaemia mortality among relatives of cystic fibrosis patients

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Abstract

A total of 219 families of patients with cystic fibrosis living in Wales were studied for the occurrence of other diseases and for cause of death, and the findings in relation to leukaemia are reported. There were eight deaths due to leukaemia, five of the myeloid type, in first and second degree relatives; this is significantly more than the expected on the basis of national age specific mortality rates. In comparison, mortality among siblings, parents, aunts and uncles, and grandparents from all causes was within the expected. Screening the five patients with myeloid leukaemia for the delta F508 mutation showed that four were carriers of this mutation. It is concluded that carriers of the delta F508 mutation may have an increased risk of developing acute myeloid leukaemia. This could happen through the direct effect of the cystic fibrosis gene itself, or through its influence on another gene, such as the met oncogene, or gene(s) involved in granulocyte function on the long arm of chromosome 7.

Cystic fibrosis is inherited as an autosomal recessive disease for which the most common gene mutation, delta F508, has been defined on 7q31.[1] In view of the relative frequency of cystic fibrosis,[2] its variable clinical features, and the multisystem involvement, an association with other diseases might be expected.

As part of a systematic clinical and molecular genetic study of this disorder in Wales a specific inquiry was made about the incidence of various diseases in patients and their relatives. In 1989, we published a preliminary report on this survey showing an increased mortality from leukaemia among first and second degree relatives of 130 families of patients with cystic fibrosis living in Wales.[3] Since then 89 other families have been studied. We report here the principal findings of the whole survey.

Patients and methods

A genetic survey of families of patients with cystic fibrosis in Wales was carried out over a period of 28 months (June 1987–September 1989). Altogether 219 families of 230 patients, representing 75% of all patients with cystic fibrosis living in different parts of Wales, were studied as part of a formal genetic study, set up mainly in order to provide genetic counselling. No bias was exercised in the selection of patients for this study; all were seen during the usual cystic fibrosis clinic sessions when they attended for routine clinical follow up. The diagnosis of cystic fibrosis had been made by the paediatrician, based on typical clinical presentation and features, family history in some cases, and at least one positive sweat test. Multigeneration pedigree and detailed family history were obtained, including age if alive on January 1988, age at death and cause of death (if known), or age at 'lost to follow up'.

Data on first and second degree relatives were included and grouped as: siblings, half siblings, parents, aunts and uncles, and grandparents.

The expected and observed numbers of deaths were compared for leukaemia of all types, myeloid leukaemia, and all causes combined. The expected numbers of deaths were obtained by multiplying for each group person years at risk by age (0–4, 5–14, 15–24, etc) with the age specific mortality for England and Wales (1979–88) for leukaemia, myeloid leukaemia, and all causes combined.[4] Parents and grandparents of patients with cystic fibrosis had to have survived to reproductive age and the generation intervals for these families average 24·4 years: accordingly person years at risk and expected mortality for parents and grandparents have been estimated from age 24. Siblings, aunts and uncles, however, were at risk of infant and early childhood death, and older aunts and uncles were at risk of higher death rates earlier in the century. Accordingly person years at risk of death and the expected mortality for those aged <5 years were estimated on a cohort of birth basis (in decades). The observed numbers of deaths were compared with the expected, using the Poisson probability distribution.

Carrier status of the eight relatives who died of leukaemia was sought; DNA was extracted from bone marrow slides of three relatives. DNA was also extracted from all relevant members of these families, and they were screened for the most common cystic fibrosis mutation in Britain, delta F508, by amplification of genomic DNA by the polymerase chain reaction.[5] Separation of polymerase chain reaction products was by polyacrylamide gel electrophoresis allowing identification of carriers.

All cases of leukaemia were verified from the original haematological studies.

Results

The families of 230 patients with cystic fibrosis living in Wales were interviewed by LNAJ, identifying 438 parents, 227 siblings, 96 half siblings, 1252 aunts and uncles, and 869 grandparents..

Eight first and second degree relatives of patients with cystic fibrosis had died of leukaemia: five with acute myeloid leukaemia, two with acute lymphoblastic leukaemia, and one with chronic lymphatic leukaemia. A grandfather suffering from chronic lymphatic leukaemia, who was alive, was not included in the study. Information on age (alive, lost to follow up, or dead) was incomplete for 7% of aunts and uncles and 11% of grandparents; these were assigned according to the age distribution of the appropriate group. The expected number of leukaemia deaths for all relatives combined was (3·1) compared with the observed number (8) using the Poisson probability test as shown in table 1 (p<0·02).

Table 1 The expected and observed number of leukaemia deaths among first and second degree relatives of patients with cystic fibrosis

Relationship	*No at risk*	*Expected† deaths*	*Observed deaths*
Sibling	227	0·06	0
Half sibling	96	0·02	1
Parent‡	438	0·15‡	2
Aunt or uncle	1252	0·98	2
Grandparent‡	869	1·87‡	3
Total	2882	3·1*	8*

*p<0·02.
†On the basis of age specific death rates for England and Wales 1979–88.
‡For parents and grandparents, person years at risk and expected mortality has been determined from age 24.

Table 2 The expected and observed number of deaths from acute myeloid leukaemia among first and second degree relatives of patients with cystic fibrosis

Relationship	*No at risk*	*Expected† deaths*	*Observed deaths*
Sibling	227	0·01	0
Half sibling	96	0·01	0
Parent‡	438	0·10‡	2
Aunt or uncle	1252	0·47	1
Grandparent‡	869	1·13‡	2
Total	2882	1·7*	5*

*p<0·05.
†On the basis of age specific death rates for England and Wales 1979–88.
‡For parents and grandparents, person years at risk and expected mortality has been determined from age 24.

The expected numbers of deaths from myeloid leukaemia among relatives of patients with cystic fibrosis were also calculated as shown in table 2. The expected number of deaths (1·7) was compared with the observed number (5) using the Poisson probability distribution (p<0·05). These figures for both leukaemia and myeloid leukaemia become slightly more significant if account is taken of the standardised mortality ratio for leukaemia in Wales (0·93) compared with England and Wales (1·00) during the reference period.

Table 3 sets out details of the eight relatives who died of leukaemia in our survey. Case 5 had myelodysplastic syndrome which progressed to acute myeloid leukaemia before his death. Patients were from different families, apart from cases 3 and 4, who were father and daughter. Screening the five patients with acute myeloid leukaemia for the delta F508 showed that four were carriers of this mutation (three by polymerase chain reaction amplification of bone marrow specimens and slides and one by inference from the rest of the family). Though we could not confirm mutational status in the fifth patient (case 4), either by inference or actual screening of haematological specimens, he had a 50% chance of carrying the same mutation. Chromosomal study was done from bone marrow aspirate on three of the patients with acute myeloid leukaemia.

The observed mortality from all causes was within the expected for siblings, parents, aunts and uncles, and grandparents (table 4).

Table 4 All cause mortality in first and second degree relatives of patients with cystic fibrosis

Relationship	*No at risk*	*Expected‡ deaths*	*Observed deaths*
Sibling	227	3·7	7
Half sibling	96	1·4	4
Parent*	438	8·9*	10
Aunt or uncle†	1252	108	92
Grandparent*	869	247*	264

*For parents and grandparents, person years at risk and expected mortality have been determined from age 24.
†For aunts and uncles, early mortality (age <5 years) has been determined by decade cohorts.
‡On the basis of age specific death rates for England and Wales 1979–88.

Table 3 Individual details of the leukaemia cases

Case No	*Relationship*	*Age at death*	*Year of death*	*Presence (+) or absence (−) of delta F508 mutation*	*Karyotype**	*Diagnosis*
1	Father	42	1981	+	XY 46	Acute myeloid leukaemia
2	Mother	37	1986	+	XX 46	Acute myeloid leukaemia
3	Aunt	55	1975	(+)†	ND	Acute myeloid leukaemia
4	Grandfather	73	1954	?	ND	Acute myeloid leukaemia
5	Grandfather	78	1988	+	X 45	Acute myeloid leukaemia
6	Uncle	3	1967	?	ND	Acute lymphoblastic leukaemia
7	Half sister	2	1987	−	‡	Acute lymphoblastic leukaemia
8	Grandfather	75	1975	+	ND	Chronic lymphatic leukaemia

*Karyotype done once at diagnosis.
†(+) Carrier status by inference.
‡46XX/55XX, +4, +6, +8, +10, +14, +17, +18, +21, +21.
? 50% risk of carrying the delta F508 mutation.
ND, not done.

Discussion

Our previous preliminary report showed an excess mortality from leukaemia among first and second degree relatives of patients with cystic fibrosis and the excess was most striking for parents, who are obligatory carriers of the cystic fibrosis gene.[3] The present report on 75% of the Welsh families with a patient with cystic fibrosis still shows an excess mortality from leukaemia and most particularly that the excess was of the myeloid type.

Although the survey has revealed a further living leukaemia case, he is not included in this study as the analysis is of mortality. We also have confirmed that four out of the five patients with acute myeloid leukaemia were carrying the delta F508 mutation.

As this survey was based on a genetic counselling service for families and the analysis is primarily of relatives of living patients with cystic fibrosis, mortality among the patients themselves has not been included in the analysis composition. Although no leukaemia deaths were found among deceased patients with cystic fibrosis in our survey, leukaemia has been reported previously in patients with cystic fibrosis: four children and two adults, three of whom had acute myeloid leukaemia, though acute lymphoblastic leukaemia would be expected to predominate in their age group.[6] As infection remains a major cause of death in patients with cystic fibrosis and serious infection is not unexpected, Biggs and colleagues questioned whether death may occur in early phase of leukaemia, and compared the previous lack of recognition of acute leukaemia in patients with cystic fibrosis to the under-reported incidence of leukaemia in general before the antibiotic era.[6] They also discussed whether the prolonged survival of patients with cystic fibrosis would result in recognition of a predisposition to leukaemia.

Monosomy for chromosome 7 and partial deletion of the chromosome 7 long arm (7q−) are among the common recurring clonal chromosome abnormalities observed in bone marrow cells in patients with acute non-lymphocytic leukaemia or myelodysplastic syndrome.[7] The loss of all or part of chromosome 7 long arm has seen associated with a granulocyte chemotaxis defect, a susceptibility to infections, a rapid progression of the disease, and a poor response to treatment.[8] Patients with a 7q− chromosome had a deletion breakpoint in a narrow region between the erythropoietin and plasminogen activator type 1 genes on either side of the cystic fibrosis gene locus.[7] Bone marrow monosomy 7 in children has been associated with a distinct myeloproliferative syndrome that usually evolves into acute myeloid leukaemia. It also appears that a significant incidence (up to 30%) of monosomy 7 in children may be familial.[9]

Met oncogene mapped to band 7q21–31, is closely linked to the cystic fibrosis gene.[10] Its activation through a DNA rearrangement resulting in the fusion of a translocated promoter region locus on chromosome 1 to the 5′ region of sequences derived from the met locus on chromosome 7, is known to occur in vitro when human osteogenic sarcoma cell line is treated with a chemical carcinogen (N-methyl-N-nitro-N-nitrosoguanidine).[11] Met is also amplified and overexpressed in the human gastric tumour cell line,[12] adenocarcinoma of the pancreas, and adenocarcinoma of the colon among a few other non-haemopoietic tumour cell lines tested.[13] Similarity has been noted in the strucuture of the activated met gene with that of the activated abl gene involved in Philadelphia chromosomal translocation occurring in chronic myeloid leukaemia,[13] suggesting that these genes encode aberrant tyrosine kinases that do not respond to normal cellular control mechanisms.[14]

We conclude that carriers of the delta F508 mutation in the cystic fibrosis gene may have an increased risk of developing acute myeloid leukaemia. This could be through the direct effect of the gene or gene product itself or through its influence on another gene, such as the met oncogene, or gene(s) involved in granulocyte function on the long arm of chromosome 7. This influence might occur by the somatic loss of a tumour suppressor gene on the homologous chromosome 7, either through gross chromosomal rearrangements or point mutations.

As a follow up to our study an analysis of all acute myeloid leukaemia patients for frequency of the delta F508 mutation is now being carried out at the University Hospital of Wales. This should give information on whether our findings are of more general relevance outside families affected with cystic fibrosis.

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Fetal phenytoin exposure, hypoplastic nails, and jitteriness

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Abstract

In a prospective study infants born to mothers with epilepsy (n=61) were found to have an unexpectedly high incidence of congenital anomalies (26/61, 43%) and neonatal conditions (26/61, 43%) compared with controls (0/62, and 6/62, 10%, respectively). There were two neonatal deaths in the study group but none among the controls. Hypoplasia of the finger or toenails was a common congenital anomaly in those infants whose mothers had received phenytoin alone or in combination with other anticonvulsant drugs (11 of 40, 28%). The mean serum phenytoin concentration was higher among mothers of infants with hypoplastic nails than among those with normal nails. Jitteriness was a common neonatal condition affecting infants of epileptic mothers (11 of 61, 18%) but not controls. The mean cord serum phenytoin concentrations were similar among jittery and non-jittery infants. At follow up (after excluding one infant with Down's syndrome from the study group) the infants seemed to have developed normally, though one had serious learning difficulties at school. We suggest that hypoplasia of the nails is related to high maternal serum concentrations of phenytoin, and though 18% of infants born to epileptic mothers were jittery compared with no control infants this may not be the result of withdrawal of the drug in all cases.

An excess of relatively minor congenital anomalies has been reported among children of epileptic mothers[1–4] as well as serious defects such as cardiovascular malformations, cleft lip or palate, and inguinal hernia.[2, 5, 6] The minor congenital anomalies include hypoplastic nails, distal phalangeal hypoplasia, epicanthic folds, hypertelorism, long philtrum, abnormal ears, and low hairline.[4] A combination of some of these features associated with microcephaly, growth deficiency, and mental retardation has been identified in infants of mothers treated with phenytoin and has been called the 'fetal hydantoin syndrome'.[7] Though exposure to anticonvulsant drugs has been suggested as a cause of these anomalies[3, 8, 9] some of them may be genetically linked to epilepsy.[4, 10]

Various neonatal conditions have been described in infants born to epileptic mothers, including irritability,[2, 11] gingival hyperplasia,[2] and haemorrhage as a result of a coagulation defect.[12] The irritability may have been a symptom of withdrawal of the drug at birth.[13]

In the present study the incidence of congenital anomalies and neonatal conditions in infants born to epileptic mothers were compared with those in a control group born to mothers without epilepsy. Hypoplasia of the finger and toenails and jitteriness, which were commonly seen in infants of epileptic mothers, were related to phenytoin concentrations in maternal blood and cord blood, respectively. Infants of epileptic mothers and of controls were followed up at outpatient clinics.

Patients and methods

MOTHERS

A group of pregnant mothers each of whom gave a history of grand mal epilepsy and who were referred to our antenatal clinic from 1 September 1980 to 31 August 1982 were included in the study. They attended a special clinic every two weeks for routine hospital antenatal care, clinical assessment of seizure control, and adjustment of anticonvulsant dosage in accordance with serum drug concentration or clinical response. Control mothers were selected at the time of antenatal booking and were matched for maternal age, parity, and social class. There were no heavy smokers (defined as smoking more than 20 cigarettes/day), none had medical complications such as diabetes or hypertension, and none of the control mothers were taking any drugs regularly. Folic acid (15 mg/day) was prescribed for all mothers. The groups were comparable (table 1).

ANTICONVULSANT DRUGS

Maternal serum drug concentrations were maintained within therapeutic ranges for phenytoin

Table 1 Infants born to epileptic mothers and controls

	Infants of epileptic mothers (n=61)	*Controls (n=62)*
Mean (SD) maternal age (years)	26·5 (4·9)	26·6 (4·8)
Mode of delivery:		
Spontaneous vaginal	37	40
Forceps	5	10
Caesarean section	19	12
Gestational age (weeks):		
Preterm (28–36)	8	3
Full term (37–42)	53	59
Birth weight (g):		
1080–2499	8	3
2500–4600	53	59
Small for dates	2	2
Occipitofrontal head circumference (cm):		
28·0–32·9	14	7
33·01–35·9	36	38
36·0–39·9	11	17
Congenital anomalies:	26**	0
Neonatal complications	26**	6

**p<0·001, Fisher's exact test.

Table 2 Congenital anomalies among 61 infants of epileptic mothers

	Single drug throughout pregnancy					*Drugs only in first trimester*			*Combinations of drugs†*	*No drugs*	*Total*	*Controls*
	Phenytoin	*Carbemazepine*	*Phenobarbitone*	*Valproate*	*Clonazepam*	*Phenytoin*	*Phenobarbitone*	*Valproate*				
No of infants	22	3	4	1	1	1	2	1	18	8	61	62
Total No with congenital anomalies:	12	2	1	0	0	0	0	0	10	1	26**	0
Cranial nerve palsy	—	1	1	—	—	—	—	—	—	—	2	—
Epicanthic folds	1	—	—	—	—	—	—	—	2	—	3	—
Extra digits	1	1	—	—	—	—	—	—	—	—	2	—
Flattened bridge of nose and hypertelorism	—	—	—	—	—	—	—	—	1	—	1	—
Heart disease	1	—	1	—	—	—	—	—	2	1	5	—
Dislocation of hip	1	—	—	—	—	—	—	—	—	—	1	—
Hypoplastic nails	5	—	—	—	—	—	—	—	6	—	11*	—
Distal phalangeal hypoplasia	1	—	—	—	—	—	—	—	2	—	3	—
Hypospadias	1	—	—	—	—	—	—	—	—	—	1	—
Inguinal hernia	—	—	—	—	—	—	—	—	1	—	1	—
Ptosis	1	—	—	—	—	—	—	—	—	—	1	—
Craniosynostosis (saggital suture)	2	—	—	—	—	—	—	—	—	—	2	—
Transverse palmar crease	—	—	—	—	—	—	—	—	2	—	2	—
Down's syndrome	1	—	—	—	—	—	—	—	—	—	1	—

$^{*}p<0{\cdot}05$, $^{**}p<0{\cdot}001$ (Fisher's exact test).
†Combinations included phenytoin, carbamazepine, phenobarbitone, primidone, valproate, clonazepam, and sulthiame.
0, No infants with congenital anomalies.
—, Absence of a particular congenital anomaly.

(10–25 mg/l),[14] carbamazepine (4–10 mg/l),[15] and phenobarbitone (10–40 mg/l)[15 16] by adjustment of dosage. In early pregnancy (gestational age less than 20 weeks) we tried to keep the serum drug concentration in the low to middle part of the therapeutic range but in later pregnancy (to offset an expected rise in the frequency of seizures) the doses were increased to achieve concentrations in the middle to upper part of the therapeutic range. Serum drug concentrations were determined by high performance liquid chromatography (HPLC) by the methods of Adams and Vandemark,[17] and Kabra *et al.*[18] In the relatively small number of mothers who were taking valproate, sulthiame, or clonazepam (table 2) serum drug concentrations were not routinely measured. The dose of the drug was adjusted as recommended in the *British National Formulary* to achieve control of seizures.[19] If the control deteriorated, the mother was admitted to hospital for neurological investigations and stabilisation. Such mothers sometimes required additional loading doses of anticonvulsant drugs.

INFANTS

Each infant's condition at birth was assessed by a subset of the Apgar scoring method.[20] A segment of umbilical cord was clamped and venous blood was collected for serum phenytoin estimation. Birth weights were measured by a beam balance. The occipitofrontal head circumference was measured with a paper measuring tape. Gestational age, calculated from the first day of the last menstrual period, was checked by assessment of various neurological and external characteristics in each newborn infant.[21] Each infant was examined by a paediatrician (SWD'S) and a geneticist (DD), neither of whom was aware of whether the mother was in the study group or the control group. Infants were deemed 'small for dates' if their birth weights were less than the third centile for gestational age.[22] In later childhood the children were assessed for developmental delay (developmental quotient less than 70) using Griffiths's mental developmental scales when they were between 2·5 and 3·5 years old.[23] Information was obtained from parents and, where possible, school teachers about learning difficulties at school between 1986 and 1989.

STATISTICAL ANALYSIS

The data were analysed with Student's t test, Fisher's exact test, or the χ^2 test. A probability of $<0{\cdot}05$ was accepted as significant.

Results

With one exception the infants born to mothers with epilepsy (study group) and the controls were in a good condition at birth,[20] and required only routine care. The one exception was an infant who was born to a mother who had an epileptic fit during labour; this infant gasped at birth and after oxygen was administered by face mask regular respirations were established within a five minute period. Mean maternal age and details of the infants are shown in table 1. The proportions of preterm infants in both groups were statistically similar. In the study group, three preterm infants had gestational ages of 28 to 32 weeks, and the remaining five infants had gestational ages of 33 to 36 weeks. In the control group, the gestational ages of the three preterm infants were 33 to 36 weeks. More infants in the study group had congenital anomalies or neonatal conditions compared with controls.

CONGENITAL ANOMALIES

Twenty six of 61 infants (43%) had congenital anomalies in the study group compared with none of 62 control infants (table 2). These anomalies occurred in 15 of 31 infants (48%) whose mothers had treatment with a single drug throughout pregnancy, 10 of 18 infants (56%) whose mothers had a mixture of drugs and one (13%) of eight infants whose mothers had a history of epilepsy but received no drugs during pregnancy; none of the four infants whose mothers had had treatment with a single drug during the first trimester only were affected.

Table 3 Incidence of hypoplastic nails in infants with congenital anomalies born to mothers with epilepsy

	No with congenital anomalies		*No with no congenital anomalies*
	Total No	*No with hypoplastic nails*	
Mothers taking no drugs (n=8)	1	0	7
Mothers taking phenytoin alone or in combination (n=36)	21	11	15
Mothers taking drugs other than phenytoin (n=17)	4	0	13
Total (n=61)	26	11	35

Table 4 Mean (SD) maternal serum phenytoin concentrations (mg/l) in the second and third trimesters of pregnancy

	Infants with hypoplastic nails (n=11)	*Infants with normal nails (n=24)*	*p Value**
Second trimester	15·9 (6·0)	10·9 (4·5)	<0·05
Third trimester	20·5 (6·9)	15·6 (6·3)	<0·05
Second and third trimesters	18·2 (5·8)	13·3 (5·0)	<0·05

*Student's *t* test.
One mother who had phenytoin only during the first trimester was excluded.

Most of the infants had minor congenital abnormalities (table 2), though there were some children with major defects. One infant born to a 29 year old mother who had phenytoin throughout pregnancy had Down's syndrome. Five infants had congenital heart disease in the form of atrial septal defect (n=2), ventricular septal defect (n=1), patent ductus arteriosus (n=1), and hypoplastic left heart syndrome (n=1). Two infants had cranial nerve palsy. One infant with a right facial palsy and hypoglossal nerve palsy had been exposed to carbamazepine throughout pregnancy and was born by caesarean section. The other infant with bilateral abducent nerve palsy (associated with a patent ductus arteriosus) was born to a mother who had been taking phenobarbitone throughout pregnancy.

Hypoplasia of nails was more common than any other congenital anomaly (table 2), 11 infants (18%) being affected. Hypoplastic nails were recorded if several finger or toenails were small, brittle, and deeply set with an irregular surface and yellow discoloration. Hypoplasia of the fifth toenail, which is a common finding among newborn babies, was not recorded. All the infants with hypoplastic nails had been exposed to phenytoin in the uterus (in five it was the only drug and in six it was in combination with other anticonvulsant drugs). Infants born to epileptic mothers who were taking anticonvulsant drugs other than phenytoin, or those born to similar mothers who had not received anticonvulsant drugs, did not have hypoplastic nails (table 3). Some infants had hypoplastic nails alone, while others had hypoplastic nails in combination with other congenital anomalies including distal phalangeal hypoplasia, flattened bridge of the nose and hypertelorism, congenital heart disease, inguinal hernia, and transverse palmar crease. Table 4 shows the mean maternal serum phenytoin concentrations in infants wth hypoplastic nails compared with those in infants with normal nails. The differences in maternal phenytoin concentrations were significant in the second and third trimesters of pregnancy. Hypoplastic nails were associated with increased maternal phenytoin concentrations.

NEONATAL CONDITIONS

Neonatal conditions were diagnosed in 26 of 61 infants in the study group (43%) and six of 62 controls (10%) (table 5). 'Jitteriness' was common, being recorded in 11 infants in the study group (18%) but not among controls. Such infants seemed excitable with increased muscle tone and reflexes, tremors, and a heightened Moro reflex.[24] The jittery infants were born to mothers who had: phenytoin alone (n=2); valproate alone (n=1); a combination of drugs including carbamazepine, phenytoin, phenobarbitone, valproate, sulthiame, and primidone (n=7); and no drugs (n=1) during pregnancy.

Table 5 Neonatal conditions

	Single drug throughout pregnancy					*Drugs only in first trimester*			*Combinations of drugs†*	*No drugs*	*Total*	*Controls (n=62)*
	Phenytoin	*Carbemazepine*	*Phenobarbitone*	*Valproate*	*Clonazepam*	*Phenytoin*	*Phenobarbitone*	*Valproate*				
No of infants	22	3	4	1	1	1	2	1	18	8	61	62
Total No with neonatal conditions	11	1	0	1	0	0	0	0	11	2	26**	6
Cephalhaematoma	—	—	—	1	—	—	—	—	—	—	1	2
Conjunctivitis	2	—	—	—	—	—	—	—	—	—	2	—
Pustular rash	1	—	—	—	—	—	—	—	1	—	2	2
Feeding difficulty (tube fed)	—	—	—	—	—	—	—	—	2	—	2	—
Fits (hypocalcaemia)	—	—	—	—	—	—	—	—	1	—	1	—
Floppy (hypotonia)	2	—	—	—	—	—	—	—	—	—	2	—
Periventricular haemorrhage (germinal layer)	1	—	—	—	—	—	—	—	—	—	1	—
Jaundice	2	1	—	—	—	—	—	—	1	1	5	2
Jittery	2	—	—	1	—	—	—	—	7	1	11*	—
Apnoeic episodes	—	—	—	—	—	—	—	—	1	—	1	—
Idiopathic respiratory distress	1	—	—	—	—	—	—	—	1	—	2	—
Sepsis	1	—	—	—	—	—	—	—	1	—	2	—
Transient tachypnoea	—	—	—	—	—	—	—	—	1	—	1	—

*$p<0·05$, **$p<0·001$, Fisher's exact test.
†Combinations included phenytoin, carbamazepine, phenobarbitone, primidone, valproate, clonazepam, and sulthiame.
0, No infants with neonatal conditions.
—, Absence of a particular neonatal condition.

Among those mothers who had taken phenytoin (alone or in combination with other drugs) there was no significant difference in the mean (SD) cord blood serum phenytoin concentrations between infants with jitteriness (16·3 (7·0) mg/l, n=11) and those without jitteriness (15·7 (7·8) mg/l, n=25). All the jittery infants were in a good condition at birth and none had had birth asphyxia. One jittery infant developed tonic and clonic seizures on day 2 as a result of hypocalcaemia (serum calcium concentration 0·9 mmol/l).

There were two neonatal deaths (at 21 hours and 28 hours of age) among infants of mothers with epilepsy. The first infant was born preterm at 32 weeks' gestational age and had idiopathic respiratory distress and pneumothorax. The second infant was born at a similar gestational age and had intrauterine growth retardation and congestive heart failure caused by a hypoplastic left heart.

FOLLOW UP

Among infants with hypoplastic nails at birth, improved nail growth had taken place by 3 months of age. The jitteriness that was observed during the first three days of birth had resolved by 2 weeks. Excluding the child with Down's syndrome, none of the remaining children in the study group had a major impairment in later childhood. There were therefore no children with neuromotor impairment caused by cerebral palsy and none with sensorineural hearing loss, impaired vision, epilepsy, or developmental delay. The median (range) developmental quotients of the children of epileptic mothers (excluding the child with Down's syndrome) and of controls were 94 (75–134) and 98 (90–120), respectively. With the exception of the child with Down's syndrome (who attended a special school) the children in both groups attended normal schools. One child in the study group received special help at school for serious learning difficulties; he also had some dysmorphic features including a flattened bridge of the nose and hypertelorism.[25] These findings were associated with severe reading and spelling difficulty, impaired language development, and visuospatial defects.

Discussion

The high incidence of congenital anomalies in the present study (43%) is nearly four times that mentioned in a review of previous prospective studies of infants born to epileptic mothers.[6] This unexpected result may be the result of differences in the methods of assessment and reporting of congenital anomalies. Alternatively, the differences might have arisen because of the way we managed anticonvulsant drugs during pregnancy; doses were increased as gestational age advanced to maintain serum concentrations of phenytoin, phenobarbitone, and carbamazepine within a 'therapeutic range' and to reduce the risk of epileptic fits during pregnancy. This could, however, have influenced fetal growth and development only in the second and third trimesters of pregnancy. Because organogenesis during the first trimester would not have been affected we had expected the incidence of congenital anomalies to be similar to that previously reported. It has been suggested that folate supplements may have a protective effect if the teratogenic effect of anticonvulsants is caused by folate antagonism.[5] In our study it is doubtful whether giving such supplements was of any benefit, either because folic acid was prescribed too late or because the congenital abnormalities were not mediated by folate antagonism.

Most of the congenital anomalies we observed are common among infants of epileptic mothers. Nevertheless, there are certain differences between this and other studies. Firstly, hypoplastic nails were more common than any other congenital anomaly in our study, while previous studies have reported medial epicanthic folds, a large anterior and posterior fontanelle, or a broad nasal bridge as being more common in such infants.[2 4] Secondly, there were no cases of orofacial clefts in the present study. In contrast, a similar anomaly had increased roughly tenfold in infants of epileptic mothers.[26] Thirdly, cranial nerve anomalies—which were found in two (3%) of our infants of epileptic mothers—have not previously been reported. The present findings have raised the possibility of agenesis of the cranial nerve nuclei as a result of fetal exposure to carbamazepine or phenobarbitone.[27] Fourthly, one infant with Down's syndrome was born to a 29 year old mother in the study group. At this maternal age the incidence of liveborn infants with Down's syndrome is about 1:935 but it is not known whether the incidence is affected by maternal epilepsy or anticonvulsant treatment.[28]

In the present study hypoplastic nails resulting from treatment with phenytoin in pregnancy were associated with higher mean maternal phenytoin concentrations in the second and third trimesters. It appeared that hypoplasia of the nails was dependent on differences in maternal serum phenytoin concentrations within the range 10–25 mg/l.[14] It is not clear why phenytoin should affect nails particularly, and not all the other ectodermal structures in these infants. In contrast Gaily *et al* reported hypoplastic nails among infants of epileptic mothers who had been on other anticonvulsant drugs (excluding phenytoin) as well as among infants of epileptic mothers who had not taken drugs during pregnancy.[4] It would seem, therefore, that there may be an appreciable genetic influence that contributes to the development of hypoplastic nails in addition to the effect of phenytoin. The possibility of interactions between genetic factors and drugs may mean that anticonvulsant drugs have teratogenic effects in some infants but not in others.[3]

Neonatal jitteriness may result from withdrawal of the drug.[13] It was observed in our infants within a three day period of birth, and did not seem to be related to a specific drug or to cord serum phenytoin concentrations. In addition, our study has shown that jitteriness occurred in one of eight infants born to epileptic mothers who did not receive drugs during pregnancy. This raises the possibility that there are other causes of jitteriness including a reduced calcium concentration such as occurred in one infant who developed tonic and clonic seizures.

Although an increased incidence of various congenital anomalies and neonatal conditions was observed in the infants born to epileptic mothers, those infants who survived seemed to do so without major impairments though one of them had a serious learning disability. We are aware that Gaily *et al* have recently reported that in spite of equal general intelligence the children of epileptic mothers had impaired visuospatial, auditory and speaking skills compared with children of non-epileptic mothers.[29] In addition, these authors suggested that children of epileptic mothers have an increased risk of specific cognitive dysfunction that contributes to learning difficulty.

Our study raises the possibility that maintaining maternal drug concentrations within a 'therapeutic' range may have benefited the infants in preventing some serious congenital malformations; there were none with orofacial clefts. Unfortunately maternal drug concentrations were not monitored near the time of conception or in the first few days after conception. From the information we have about maternal drug concentrations it is not possible to draw any conclusions about the relative risks of congenital abnormalities with different anticonvulsant drugs. Monitoring maternal serum anticonvulsant concentrations did not prevent neonatal deaths. Hypoplastic nails and jitteriness in these infants did not seem to have any serious long term effects.

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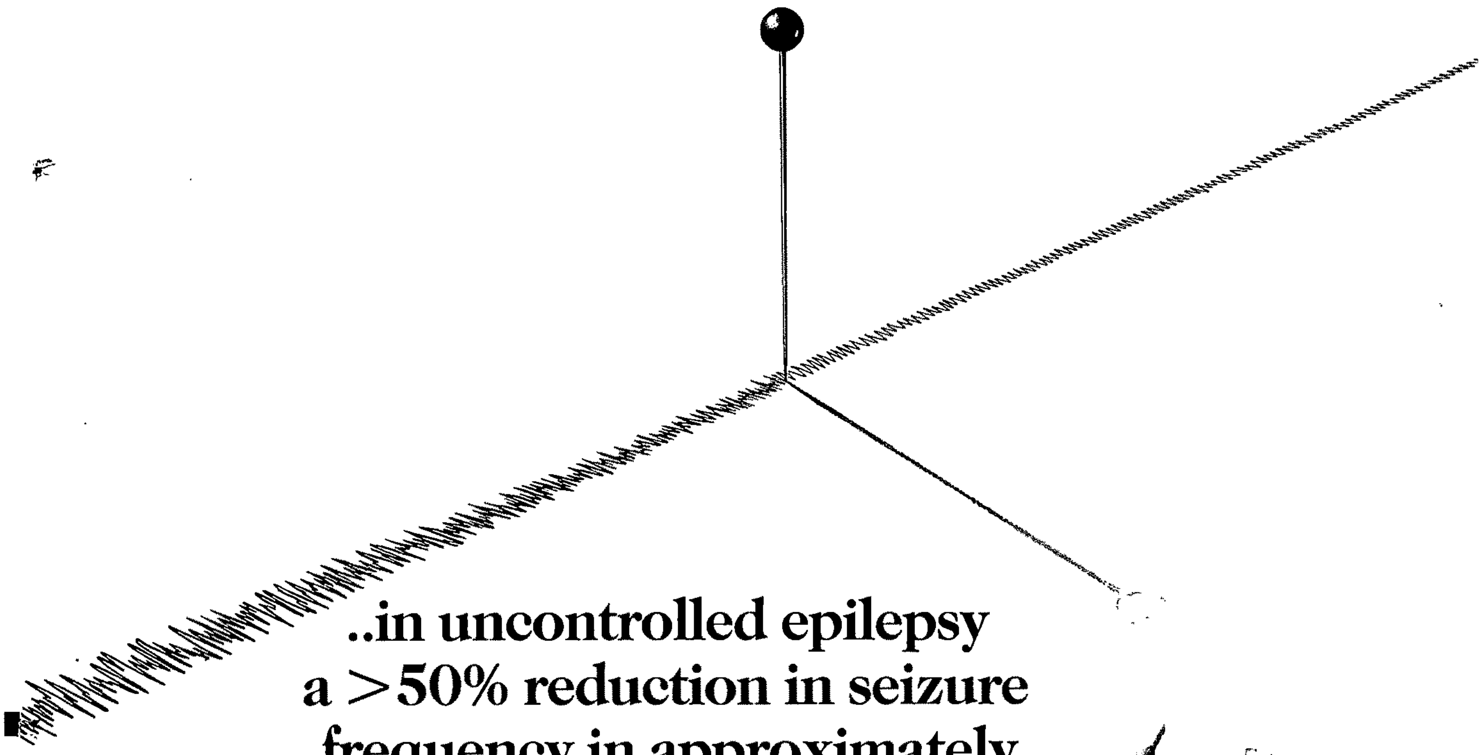

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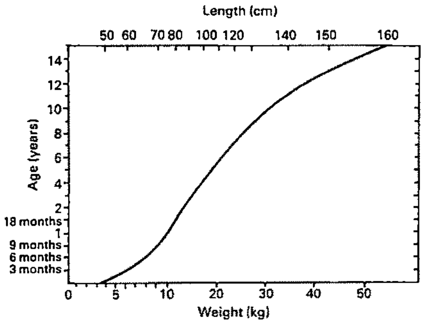
DOW**

Endotracheal tube

Length (cm)	Internal diameter (mm)
18–21	7·5–8·0
18	7·0
17	6·5
16	6·0
15	5·5
14	5·0
13	4·5
12	4·0 3·5
10	3·0–3·5

Paediatric resuscitation chart



Adrenaline (ml of 1/10 000) intravenous or endotracheal	0·5	1	2	3	4	5
Atropine (mg) intravenous or endotracheal	0·1	0·2	0·4	0·6	0·6	0·6
Bicarbonate (ml of 8·4%) intravenous	5	10	20	30	40	50
Calcium chloride (mmol)* intravenous	1	2	4	6	8	10
Diazepam (mg) intravenous per rectum	1·25 2·5	2·5 5	5 10	7·5 —	10 —	10 —
Glucose (ml of 50%) intravenous	10	20	40	60	80	100
Lignocaine (mg) intravenous or endotracheal	5	10	20	30	40	50
Salbutamol (μg) intravenous	25	50	100	150	200	250
Initial DC defibrillation (J)	10	20	40	60	80	100
Initial fluid infusion in hypovolaemic shock (ml)	50	100	200	300	400	500

* One millilitre calcium chloride 1 mmol/ml ≡ 1·5 ml calcium chloride 10% ≡ 4·5 ml calcium gluconate 10%

A child is dying: what do you do?

Resuscitating children is different from resuscitating adults—and more difficult. Because cardiorespiratory arrest in children is uncommon each doctor's experience of handling it is limited, and there is a tendency to forget the recommended drug doses; also, because children come in so many different sizes it is hard to judge the correct dose, especially if you do not know the child's weight. Yet delay or inaccuracy in treatment might be fatal. **The Paediatric Resuscitation Chart,** devised by Dr Peter Oakley and based on the guidelines of the Resuscitation Council (UK), gives you at a glance the essential information for making rapid and accurate decisions. The chart is available as an A2 size poster or a pocket sized postcard.

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Single copies of a postcard version of the chart are available, free of charge, on receipt of an A5 stamped addressed envelope (16cm x 24cm; 6in x 9in). Bulk orders please write to the Book Department.
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Certified cause of death in children and young adults with cerebral palsy

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Abstract

The status of 732 children suffering from cerebral palsy from the South East Thames region (births from 1970–9) was ascertained at the end of 1989, and copies of death certificates of the 73 children who have died, aged 4 weeks to nearly 16 years, were obtained. Infantile cerebral palsy (ICD Code 343-) was coded as the underlying cause of death in only 16 (22%) cases. On 28 (38%) certificates there was no mention of any form of cerebral palsy, the proportion in which it was not mentioned increasing with age. In 20 (28%) cases the coded underlying cause of death was respiratory, hence in published national statistics the number of deaths from respiratory causes is inflated. A postmortem examination was known to have been performed in 23 cases, but the recorded information was in some cases limited to a 'terminal event'. The importance of good data on the death certificate, and the significance of published national statistics, need to be communicated to all those involved in the certification process if cerebral palsy and other chronic conditions, which raise the relative risk of death, are not to be under-represented.

The under-representation of chronic 'non-fatal' diseases in mortality statistics has been documented.[1, 2] The life expectancy, the cause of death, and its antecedent causes in individuals suffering from cerebral palsy are of interest to those seeking to ensure that their long term needs are provided for. If cerebral palsy is similarly under-represented, however, published national statistics based upon death certificate data might lead to misleading conclusions.

The South East Thames region cerebral palsy register (births from 1970–9) has provided the cases for a population based view of survival of those suffering from the various types of cerebral palsy with different degrees of impairment. This paper presents the data obtained from death certificate copies relating to 73 children who have died.

Methods

The South East Thames cerebral palsy register (births from 1970–9) was assembled between 1978 and 1981 using multiple sources of ascertainment. A more detailed description of the methodology of this study may be found elsewhere.[3] A total of 732 cases, of whom 420 were male and 312 were female, were traced again in 1988, mainly through the National Health Service Central Register (NHSCR) at Southport. By the end of 1989, 73 children (47 boys and 26 girls) were known to have died, at ages ranging from 4 weeks to 15·8 years. Survival analysis is published elsewhere.[4]

Copies of the death certificates have been received from NHSCR for the 73 cases who have died. These show the certified cause of death and any causes antecedent to it in part I of the certificate, contributory cause(s) in part II, and the coded underlying cause of death using the *International Classification of Disease* (ICD) 9th revision which is selected according to international coding procedures.

Results

Table 1 provides a full description of the cause of death information on the death certificates, plus the type of cerebral palsy as given to us by each child's paediatrician, and our explanatory comments where appropriate. In a number of cases minor spelling corrections have been made, but otherwise the data are recorded exactly as given to us, and include some obvious errors.

CEREBRAL PALSY ON DEATH CERTIFICATES

Except for deaths occurring in the years 1985 and 1986, when the Office of Population, Censuses and Surveys (OPCS) carried out multiple cause coding, only *underlying* cause of death is coded. The proportion of cases in whom some form of cerebral palsy appears somewhere on the death certificate declines with age, but the proportion in whom the underlying cause is coded as 343- follows a different pattern (see table 2).

The presentation of these figures is complicated by two factors: firstly, three cases (314, 540, and 740), all of whom died at ages less than 7 years (the diagnoses on the death certificate being spastic diplegia, spastic quadriplegia, and quadriparesis,) were allocated the underlying cause code 344- (other paralytic syndromes) for reasons that are not apparent to us; these cases are classed as having a mention of cerebral palsy on the death certificate. Secondly, two cases (964 and 965) who died aged 4 and 5 weeks were ascertained by means of a search by OPCS using underlying cause coding, but the cause was given as 'cerebral birth anoxia'; these two cases have been counted as having a mention of cerebral palsy in order to avoid confusion.

Table 1 Survival. Certified cause of death and clinical diagnosis (73 cases)

Case No	*Alive*	*Death certificate information*				*ICD code*	*Diagnosis given to us by paediatrician*	*Comment*
		Ia	*Ib*	*Ic*	*II*			
025	10·70–08·79	Acute lymphoblastic leukaemia	—	—	Epilepsy, spastic quadriplegia, severely subnormal	2040	Spastic quadriplegia	
041	07·71–04·72	Bronchopneumonia	—	—	Microcephaly, severe subnormality	485X	Cerebral palsy	
042	04·73–10·88	Cerebral failure	Microcephaly, epilepsy	Severe physical and mental subnormality	—	3181	Spastic quadriplegia	
075	08·77–05·83	Bronchopneumonia	Mental retardation	—	—	319X	Spastic quadriplegia	
076	09·71–05·86	Aspiration pneumonia	Cerebral palsy	—	—	3439	Spastic quadriplegia	
085	11·73–11·85	Bronchopneumonia	Quadriplegia	Previous meningitis	—	3229	Spastic	
119	11·76–04·85	Respiratory infection	Chronic obstructive airway disease	—	Microcephaly, epilepsy, and spastic quadriplegia	496X	Spastic quadriplegia	
140	08·71–12·78	Bronchopneumonia	—	—	Cerebral palsy	485X	Dystonic spastic quadriplegia	
146	08·75–04·84	Chickenpox	—	—	Lissencephaly	052X	Double hemiplegia	
147	08·70–03·75	Bronchopneumonia	—	—	Hydrocephalus—cerebral hypoplasia	485X	Cerebral palsy	
148	07·78–05·82	Overwhelming measles infection	—	—	Spastic quadriplegia and mental retardation	0559	Cerebral palsy	
169	02·74–01·81	Hypoxia	Chronic bronchitis	—	Severe subnormality	4919	Spastic quadriplegia	
191	10·71–11·80	Bronchopneumonia	—	—	Cerebral palsy, birth asphyxia	485X	Spastic quadriplegia	
195	05·73–04·83	Cardiac arrest	Hypotonic cerebral palsy	—	Severely subnormal	3439	Athetoid	
205	12·72–02·81	Acute bronchitis	Acute bronchitis	—	Cerebral palsy	4660	Athetoid	
211	01·74–01·76	Bilateral bronchopneumonia	Spasticity, mental retardation	—	Epilepsy	319X	Spastic quadriplegia	
215	06·70–04·75	Bronchopneumonia	—	—	Microcephaly	485X	Spastic quadriplegia	
239	10·73–01·78	Grand mal epilepsy	Cerebral palsy	—	Acute upper respiratory infection	3439	Ataxia—mixed	
245	02·70–10·76	Bronchopneumonia	—	—	Cerebral palsy	485–	Spastic quadriplegia	
247	12·72–06·79	Pneumonia	—	—	Cerebral palsy, neonatal meningitis	486–	Spastic quadriplegia	
258	09·71–01·86	Lobar pneumonia	—	—	—	481–	Spastic quadriplegia	
264	12·70–01·76	Bronchopneumonia	Primary cerebral degeneration	—	—	3319	Dystonic spastic	
267	05·77–12·79	Haemolytic streptococcal pneumonia	—	—	Spastic diplegia	4823	Severe quadriplegia	
287	08·71–01·75	Chest infection	Severe mixed cerebral palsy	—	—	3439	Dystonic mixed type	
292	02·79–01·82	Stevens-Johnson syndrome	—	—	Choreoathetoid cerebral palsy	6951	Choroathetoid	
293	01·71–08·84	A1: Primary alveolar hypoventilation syndrome	A2: Microcephaly (small brain)	—	—	7421	Spastic quadriplegia	
306	10·73–10·78	Pneumonia	Pneumonary dysplasix	Cerebral palsy	—	7485	Dystonic quadriplegia	
307	04·73–02·78	Bronchopneumonia	Spastic quadriplegia	Microcephaly	—	7421	Spastic quadriplegia	
314	01·74–04·77	Chronic renal failure	Renal tubular acidosis	Spastic diplegia, severe meckel retardation, microcephaly	—	3442	Spastic quadriplegia	'Meckel' counted as 'mental' in calculations
352	02·70–01·71	Gastroenteritis	Bronchopneumonia	—	Cerebral palsy, mental retardation	0558	Athetoid	
353	08·76–07·87	Epilepsy	Congenital hydrocephalus	—	—	7423	Spastic quadriplegia	
370	07·76–08·83	Bronchopneumonia	Epilepsy	Cerebral atrophy	—	7428, 485, 3459	Athetoid	[Scottish death certificate]
371	02·74–05·75	Resp failure	Pneumonia	—	Gross psychomotor delay, secondary epilepsy	486X	Spastic left>right	
378	03·74–03·78	A1: Cardiorespiratory failure	A2: Congenital cerebral palsy ('spasticity')	A3: Epilepsy	—	3459	Spastic quadriplegia	
384	07·72–06·73	Inhalation of vomit in association with neuromuscular disease	—	—	—	3589	Hypotonic athetoid	
387	09·72–05·74	Bronchopneumonia	Cerebral palsy	—	—	343X	Severe asymmetrical dystonic quadriplegia	
392	07·70–12·85	Reye's syndrome	—	—	—	3318	Cerebral palsy	
396	01·76–09·81	Multiple injuries (accidental death)	—	—	—	E9289, 9598	Crural monoplegia	Inquest held
431	09·73–12·81	Status epilepticus	Hydrocephalus and cerebral palsy	Neonatal meningitis	—	3229	Spastic quadriplegia+ataxia	
439	12·73–07·86	Bronchopneumonia	—	—	—	485–	Dystonic quadriplegia+athetosis	
478	03·70–01·79	Viral pneumonitis	—	—	—	4809	[No diagnosis received]	[Notified as cerebral palsy]
504	09·70–03·86	Aspiration of vomitus	Cerebral palsy	Hydrocephalus	—	3439	Spastic quadriplegia	
508	05·70–10·80	Adrenal failure due to	Adrenal hypoplasia and bronchopneumonia	—	Hydrocephalus	7591	Cerebral palsy	
525	06·77–07·88	Status epilepticus	Spastic quadriplegia (from birth)	—	Bronchopneumonia, hiatus hernia with iron deficiency anaemia	3432	Spastic quadriplegia	
533	08·71–12·74	Bronchopneumonia	Congenital heart disease	Mental retardation	—	7469	Athetoid+ataxic	
540	03·78–04·84	Respiratory insufficiency	—	—	Spastic quadriplegia and severe mental retardation	3440	Spastic quadriplegia	
563	01·78–01·80	Bronchopneumonia	—	—	Cerebral palsy	485X	Spastic quadriplegia	
575	12·77–12·86	Gastrointestinal haemorrhage	—	—	Chest infection, spastic quadriplegia	5789	Spastic quadriplegia	
596	03·73–04·81	Ependymoma of fourth ventricle	—	—	—	1915	Spastic quadriplegia	
614	06·71–03·82	Hypostatic pneumonia	Congenital hydrocephalus	—	—	7423	Spastic quadriplegia	
632	10·70–11·78	Bronchopneumonia	Gastroenteritis	Severe mental handicap due to neonatal meningitis	—	3229	Spastic quadriplegia+athetoid	
659	04·79–06·80	Acute bronchiolitis	—	—	—	4661	Spastic quadriplegia	
661	04·78–11·80	Encephalitis	—	—	Cerebral palsy	3239	Spastic quadriplegia	
686	06·72–10·73	Severe hypostatic bronchopneumonia	Septicaemia	—	—	0389	[No diagnosis received]	[Notified as cerebral palsy]
726	06·72–01·77	Bronchopneumonia	—	—	Cerebral palsy	485–	Cerebral palsy	
727	10·70–02·71	Congestive cardiac failure	Bronchopneumonia	—	Cerebral palsy	485X	Quadriplegia	
728	03·76–08·77	Epilepsy	Cerebral palsy	Microcephaly	—	7421	Cerebral palsy	
729	07·74–09·78	Bronchopneumonia	Whooping cough	—	Microcephalic spastic quadriplegia, mental retardation	0339	Spastic quadriplegia	
730	01·72–08·72	Bronchopneumonia	Cerebral palsy	Cerebral atrophy	—	3319	Cerebral palsy	
732	12·77–12·87	Asphyxia	Cerebral atrophy	—	—	3319	[No diagnosis received]	[Notified as cerebral palsy]
740	01·79–06·80	Cardiac arrest	Chest infection	Quadriparesis	Congenital infection	3440	Spastic quadriplegia	
742	09·74–06·80	Hypostatic pneumonia	Cerebral palsy	—	—	3439	Severely hypotonic	
905	12·71–10·87	Cardiorespiratory failure	Spastic quadriplegia	Cerebral palsy	—	3439	Spastic quadriplegia	
923	03·75–12·76	Meningitis (*Staphy albus*)	Chronic infection in a child with spina bifida and hydrocephalus	—	—	7410	Hydrocephalus, spina bifida, right hemiplegia	[Dubious case]
943	10·79–12·79	Bronchopneumonia	Porencephaly	—	—	7424	Porencephaly	[Notified as cerebral palsy]
959	12·70–11·71	Bronchopneumonia	—	—	Cerebral palsy	485X	Cerebral palsy	
960	12·71–04·73	Inhalation of stomach contents due to cerebral palsy	—	—	—	343X	Cerebral palsy	
961	01·70–10·71	Respiratory arrest	Spastic CP	Septicaemia	—	343X	Spastic	
962	10·70–03·72	Bronchopneumonia	Internal hydrocephalus	Cerebral palsy	—	343X	[OPCS dead case]	
963	01·70–01·73	Bronchopneumonia	Cerebral palsy	—	—	343X	[OPCS dead case]	
964	02·74–03·74	Bronchopneumonia	Epilepsy	Cerebral birth anoxia	—	343X	[OPCS dead case]	
965	04·74–05·74	(Bronchopneumonia) Status epilepticus	Irreversible cerebral anoxia at birth	—	—	343X	[OPCS dead case]	( )=cause on death certificate which was revised
966	04·74–07·74	(Pneumonia) Acute respiratory failure	—	Cerebral palsy	(Cerebral palsy)	343X	[OPCS dead case]	( )=cause on death certificate which was revised

Table 2 Cerebral palsy on the death certificate

Age at death (years)	*No of cases*	*No (%) with cerebral palsy (343-) as underlying cause*	*No (%) with mention of cerebral palsy on death certificate**
<1	9	3 (33)	7 (78)
1-<4	21	6 (29)	15 (71)
4-<7	16	2 (13)	10 (63)
7-<10	13	0	7 (54)
10-<13	7	2 (29)	3 (43)
13-16†	7	3 (43)	3 (43)
Total	73	16 (22)	45 (62)

*Includes three cases where underlying cause is coded 344-; also two cases where the cause was given as 'cerebral birth anoxia' that were coded 343-. The trend is significant ($p=0{\cdot}04$).
†The highest age at death was 15·8 years.

OTHER CEREBRAL CONDITIONS

Of the 45 cases with a mention of some form of cerebral palsy on the death certificate, 12 also had another mention of a cerebral condition other than mental subnormality or epilepsy; of the 28 cases with no mention of cerebral palsy, 16 mentioned another cerebral condition; in 12 cases neither cerebral palsy nor any other cerebral condition was mentioned. Among the 'other cerebral' conditions were microcephaly (nine cases—of which five also mentioned cerebral palsy), hydrocephaly (eight cases—of which three also mentioned cerebral palsy), and cerebral atrophy (three cases—of which two also mentioned cerebral palsy).

Also included in this group are three cases in whom previous meningitis was mentioned (85, 247, and 632). In another child (923), with spina bifida and hydrocephalus, meningitis (described as a chronic infection) was by implication present at the time of death. In another case (661) encephalitis was given as the cause without any indication as to timing, although as it was not mentioned in the information originally supplied to use by the child's paediatrician we assume that this was a late event. In one case (632) the coding failed to reflect the chronology of the condition as recorded on the death certificate. A child who died at 8 years of age was certified as follows: 1a: bronchopneumonia, 1b: gastroenteritis, 1c: severe mental handicap due to neonatal meningitis. The coded underlying cause was 3229 (meningitis, unspecified), but we are advised that it should have been 326- (late effects of intracranial abscess or pyogenic infection).

MENTAL SUBNORMALITY AND EPILEPSY

Mental subnormality or retardation featured in 15 (21%) of the death certificates, and in five of these cases there was no mention of cerebral palsy or another cerebral condition. Epilepsy was mentioned in 14 cases (19%), including three in which status epilepticus was given under section 1a.

OTHER CERTIFIED CAUSES OF DEATH

In 57 cases (78%) a respiratory (or cardiorespiratory) cause of death appeared on the death certificate, the commonest being bronchopneumonia (29 cases). In 20 cases (28%) the coded underlying cause of death was respiratory, as shown in table 3.

Table 3 Cases with respiratory underlying cause of death

ICD code	*Condition*	*No of cases*
4660	Acute bronchitis	1
4661	Acute bronchiolitis	1
4809	Viral pneumonia—unspecified	1
481-	Pneumococcal pneumonia	1
4823	Pneumonia due to streptococcus	1
485-	Bronchopneumonia, organism unspecified	11
486-	Pneumonia, organism unspecified	2
4919	Chronic bronchitis—unspecified	1
496-	Chronic airways obstruction	1
Total		20

Reye's syndrome, Stevens-Johnson syndrome, chronic renal failure due to renal tubular acidosis, acute lymphoblastic leukaemia, chicken pox, measles, and pertussis were mentioned in one case each.

In some cases, the information provided on the death certificate appears to conflict with data obtained from other sources. In one case, a 1 year old child said by the attendant clinician to be suffering from hypotonic cerebral palsy, the cause of death 'certified after postmortem without inquest' was given as inhalation of vomit in association with neuromuscular disease (coded 3589: myoneural disorders—unspecified). However, from another source we were told that at postmortem examination the doctor found 'no histological evidence of muscle disease'. One must assume that the results of the histological examination were not available at the time of certification.

POSTMORTEM EXAMINATIONS

In 23 of the 73 cases (32%) it was apparent from the copy of the death certificate supplied to us that a postmortem examination had taken place. This was usually because after the name of the certifier appeared the phrase 'after postmortem without inquest'. In one case (396), an accidental death, an inquest had taken place, but the death certificate was not particularly informative. In most cases the box containing the information about whether or not a postmortem examination had been performed had been obscured before the copy was sent to us, so we are not able to be certain that the remaining 49 cases had been certified without necropsy.

In eight (35%) of the 23 cases known to have had a postmortem examination the underlying cause of death was given as infantile cerebral palsy (343-), and there was a mention of some form of cerebral palsy in four additional cases, hence cerebral palsy appeared on 12 (52%) of certificates in this group. This contrasts with the 49 cases not known to have had a postmortem examination: only eight (16%) had the underlying cause coded as 343-, but a total of 33 (67%) had a mention of cerebral palsy on the death certificate.

In other respects also, the death certificates issued after postmortem examination are rather less informative than those where a postmortem examination is not mentioned. Particularly disappointing is the fact that in four cases a single respiratory cause of death is given with no mention of any other condition. The sole certified causes and approximate age at death of these cases are as follows: lobar pneumonia (14 years), bronchopneumonia (12 years), viral pneumonitis (8 years), and acute bronchiolitis (14 months). We have no clinical data on the 8 year old child, owing to follow up difficulties caused by his mother's remarriage, but the other three cases are known to have been both mentally and physically handicapped.

Discussion

It is the inability to obtain from published data either an estimate of the mortality associated with cerebral palsy, or a true picture of the causes of death across the whole range of affected individuals, which highlights the need for an examination of deaths from population based studies.

The under-representation of chronic 'non-fatal' diseases in mortality statistics is well recognised,[1] [2] and many of the reasons given are relevant to cerebral palsy. The balance might be redressed in part by a change to multiple cause coding, as discussed by Israel *et al* who comment[5]: 'Although the underlying cause of death is conceptually easy to understand and is a well-accepted measure of mortality, often it does not convey the complexity of the reported medical conditions at the time of death. Because most deaths are the result of more than one disease entity, a single underlying cause excludes much useful information on intervening, contributory, and even concurrent conditions'.

The practitioners who complete the death certificates, however, may be unaware of the effect that apparently trivial differences in their mode of expression may have on the categorisation of underlying cause. This problem is discussed by Leadbetter, who concludes that death certificates are completed imprecisely or inaccurately 'because of ignorance of, or failure to apply, the principles of death certification and not because relevant information is lacking.[6]

On 28 death certificates (38%) there was no mention of any form of cerebral palsy or cerebral birth anoxia, and hence even multiple cause coding would not allow these cases to be ascertained by means of death certificate data. Cerebral palsy is more likely to be mentioned on the death certificate if the child dies in the first few years of life; it is mentioned in less than half the cases dying aged 10 years or more. Most of the children in the study (90%) are still alive, and now aged between 10 and 20 years. It remains to be seen if the proportion of death certificates containing a mention of cerebral palsy continues to decline with age.

Underlying cause coding using ICD code 343- (infantile cerebral palsy) would identify only 22% of cases. One could improve the yield by searching using a greater variety of codes including ICD code 344- (other paralytic syndromes), which was unfortunately used for 7% of the cases where some form of cerebral palsy was mentioned. If cases coded under this and several other central nervous system categories (microcephaly, meningitis, encephalitis, and cerebral degeneration) had been reviewed manually it would have been possible to pick up nine of the cases not coded 343- but with some sort of cerebral palsy mentioned on the death certificate. This would predict a yield of 25 cases (35%) using underlying cause coding enhanced by manual review, which is hardly encouraging.

The fact that in 78% of cases a respiratory (or cardiorespiratory) cause of death was mentioned on the death certificate will come as no surprise to those who are in day to day contact with the severely affected individuals who account for most of the 73 documented deaths. However, the number of cases in which a respiratory illness is coded as the underlying cause of death must be of some concern. While the very young and the very old may succumb to respiratory infections, deaths from such causes in adolescence are relatively uncommon, and the fact that certificates are considered adequate without additional information is surprising.

In January 1984 there was a significant change in the guidance to OPCS coders in the use of World Health Organisation rule 3.[7] This was in order to prevent certain 'terminal events' (for example, bronchopneumonia, pneumonia, or cardiac arrest) recorded as the only cause of death in part I of the death certificate being coded as the 'underlying cause of death' if the presence of a major disease was recorded in part II. This is a logical way of preventing under-recording, especially of chronic conditions which raise the relative risk of death but which clinicians may be reluctant to cite as '*the*' cause of death. However, this change will not achieve its desired effect if the only cause of death appearing on the death certificate is a 'terminal event' such as bronchopneumonia.

It is discouraging to find that this is more likely to happen in cases where the death certificate is stated to have been completed after a postmortem examination. It appears that those responsible for assigning a cause in some postmortem cases are content to limit the expression of their findings to a 'terminal event', even in a few cases giving a detailed description of the nature and extent of the respiratory involvement while neglecting to record the frailty or distortion of the rest of the body associated with many years of immobility, which probably rendered the individual susceptible to a respiratory death. We would not wish to undervalue the use of a postmortem examination to shed light on conditions which had not been elucidated during life.[8] However, if the pathologist seeks only to demonstrate the presence of bronchopneumonia, or omits relevant necropsy findings, the cause of death given may be more misleading than an informed guess from the attendant clinician.

The consequence of such inadequacy of information is that the number of deaths from respiratory causes in children and adolescents is being inflated by deaths that should be attributed to other causes; the corollary is that the number of deaths from conditions that cause major physical and/or mental handicap is likely to be an underestimate. Duley demonstrated, in a study of 590 stillbirths and neonatal deaths, that the presence of congenital malformations was underestimated in death certificates completed without the benefit of necropsy information.[9] Valuable data from necropsy on congenital malformations, in particular those in the brain which cause some cases of cerebral palsy, may be failing 'to see the light of day' because of the preoccupation with terminal events, particularly in coroners' cases.

Even if the quality of death certificate data were improved, the information obtained would often be insufficient to provide an adequate description of the cause of death, because of the interaction of numerous antecedents before the terminal event. The collection of more detailed information about the period before death poses serious problems, however, even for a population based study. Our experience in the South East Thames region has confirmed that it is difficult to keep track of affected individuals. In addition to normal population mobility, there are transfers away from the notifying paediatrician because individuals become too old to attend a paediatric clinic, or associated with the need for residential or other care. Even paediatric departments with above average record keeping systems have found it surprisingly difficult to inform us of the whereabouts of cases now followed up elsewhere. Family practitioner committees are only able to help with those registered with a general practitioner. Moreover, given that most of the affected children are surviving to adulthood, there are ethical considerations regarding their right to be consulted about being 'followed up': their parents may have consented to the release of medical information and their inclusion upon a register 10 years ago, but a young adult is entitled to take a different view if he or she wishes.

Improvements in quality of information during life, and after death, would lead to benefits for those suffering from a wide range of conditions. It would also prevent misleading conclusions being drawn from inadequate national statistics. It is time for greater effort and, where necessary, finance, to be directed towards strengthening the weak points in the system. The 10th revision of the *International Classification of Diseases* with new coding rules and recommendations, scheduled to come into operation in 1993, may be regarded as an advance, but will only work if the aims and intentions are fully communicated to all those involved in the certification process. Meanwhile it is important to emphasise the distinction between 'certified' cause of death and 'the' cause, or more often causes, of death, in children and adults suffering from chronic conditions including cerebral palsy.

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Peak expiratory flow rate and the acute chest syndrome in homozygous sickle cell disease

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Abstract

The peak expiratory flow rate (PEFR) was studied in 20 matched pairs of children with homozygous sickle cell disease with either no episodes or six or more episodes of acute chest syndrome. The pairs were carefully matched for height and a highly significant reduction in PEFR was observed in children with multiple episodes of acute chest syndrome. Lateral and anteroposterior chest diameters and chest circumference correlated with PEFR but did not differ between index and control cases. The most likely cause of the reduced PEFR in children with multiple episodes of acute chest syndrome is an accumulating pulmonary fibrosis that decreases lung compliance.

Children with homozygous sickle cell (SS) disease are prone to the acute chest syndrome, the relative risk being four times that in normal controls by the age of 4 years.[1] The term acute chest syndrome covers a range of acute pulmonary episodes including infection, infarction, and sequestration within the pulmonary capillaries. Adults with SS disease have significant reductions in total lung capacity, vital capacity, forced vital capacity, and ratio of residual volume to total lung capacity.[2 3] Furthermore the diffusing capacity of the alveolar membrane is reduced,[2 4] the greatest reductions occurring in those with a history of pulmonary complications.[2] Peak expiratory flow rate (PEFR), which might be expected to fall with decreased lung compliance after pulmonary complications, was normal in a small study of 12 SS children and 12 controls aged 7–19 years.[5] To determine whether peak expiratory flow rate is affected by a history of pulmonary complications, the PEFR has been studied in 20 matched pairs with SS disease, with and without histories of pulmonary complications.

Patients and methods

The patients attended the sickle cell clinic of the University Hospital of the West Indies, Kingston, Jamaica, and were participating in a cohort study of sickle cell disease from birth. Between June 1973 and December 1981, 100 000 consecutive normal deliveries at the main government maternity hospital (Victoria Jubilee Hospital) were screened. A total of 314 babies with SS disease were detected and they have been followed up prospectively. Of these 55 have died and 31 have emigrated, leaving 228 children at the study date (December 1989/January 1990) aged from 8–16 years. The diagnosis of SS disease was based on standard critiera.

The acute chest syndrome was defined as acute pulmonary symptoms associated with either clinical signs of parenchymal involvement or pulmonary infiltrates on radiography. The frequency of these events was derived by review of the computerised clinical codings and confirmed by examination of patient records. Children with asthma, bronchitis, and who had suffered a stroke were excluded. If two events were separated by less than four weeks the records were reviewed to distinguish a prolonged single event from two separate events. The number of episodes of acute chest syndrome varied from nil to 16 and 31 subjects had had six episodes or more (fig 1). Of these 31 subjects, three had chronic disease possibly influencing lung function (systemic lupus erythematosus, nephrotic syndrome, and recurrent sepsis) and were excluded and three had defaulted leaving 25 cases. It was possible to match 20 of these index cases with 20 children who had never had acute chest syndrome (control group). Each pair was matched for sex, height, and age (in order of priority).

Height was measured, without shoes, with a Harpenden wall mounted stadiometer or a portable stadiometer (checked against the fixed model) for home visits. Anteroposterior and lateral chest diameters were measured with Harpenden chest calipers in the horizontal plane through the fourth sternocostal junction at the end of normal expiration. Chest circumference was measured at the same level and stage of expiration with a standard tape measure. PEFR was measured with a portable peak flow meter

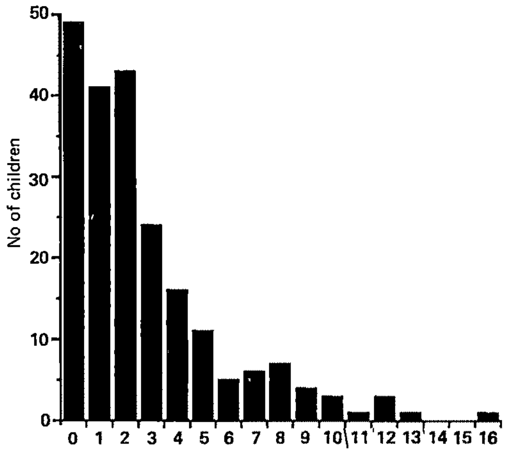

Figure 1 Frequency distribution of episodes of acute chest syndrome in children with SS disease.

(Mini-Wright, Airmed, Clement-Clarke International) in the standing position and taking the maximum of five successive measurements. The instrument was not independently calibrated but the same instrument was used for the complete study. No other aspect of pulmonary function was measured.

The paired Student's *t* test was used to compare mean values between the index cases and the controls. Correlations were assessed by the product moment correlation coefficient.

Results

The mean age of index cases, 12·1 years (range 8–16 years), did not differ from that in controls, 11·6 years (range 8–16). Mean height in index cases, 142·4 cm (range 117·5–160·0) was similar to that in controls, 143·3 cm (range 121·0–169·0).

CHEST SIZE

Chest circumference varied from 52–74 cm but did not differ between index cases (mean (SD) 62·0 (6·2) cm) and controls (63·8 (5·4) cm). Chest circumference was significantly correlated (r=0·66 p<0·001) with PEFR (fig 2).

CHEST SHAPE

Anteroposterior chest diameter varied from 12·2–18·9 cm but did not differ between index cases (mean (SD) 14·7 (1·5) cm) and controls (14·6 (1·3) cm). Lateral chest diameters varied from 16·6–24·6 cm and also did not vary between index cases (20·2 (1·8)) and controls (20·6 (1·9)). Both measurements correlated with PEFR (figs 3 and 4), although the correlation was closer with lateral diameter (r=0·69, p<0·001) than with anteroposterior chest diameter (r=0·43, p<0·01).

The abnormal anthropometry of SS disease affects chest shape by reducing the lateral chest diameter and making a more hoop shaped chest with an increased ratio of anteroposterior to lateral chest diameter. To ascertain whether this abnormal shape determined the abnormalities in PEFR, the association between this ratio and the PEFR was assessed. The ratio did not differ between index cases (mean 1·38 (0·11)) and controls (1·41 (0·11)) and did not correlate with the PEFR (r=0·07, p>0·1).

PEFR

As expected, the PEFR increased with height in both index cases and controls,[6] although values were consistently lower in patients with a history of pulmonary complications (fig 5). The difference in PEFR between matched pairs (mean 63·8 (33·4); range 10–120 l/min) was significant (paired *t* test, t=8·55, p<0·001). Overall the PEFR in index cases (mean 291 (50);

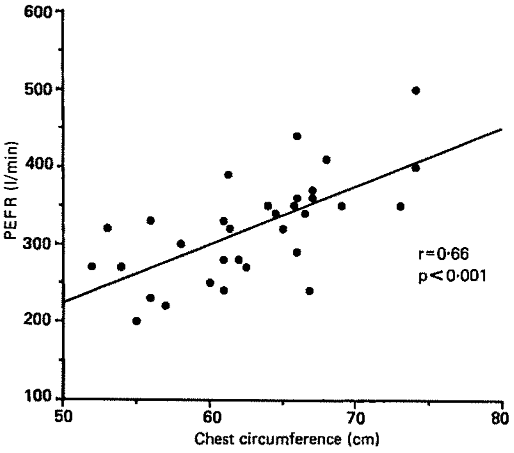

Figure 2 Association between PEFR and chest circumference.

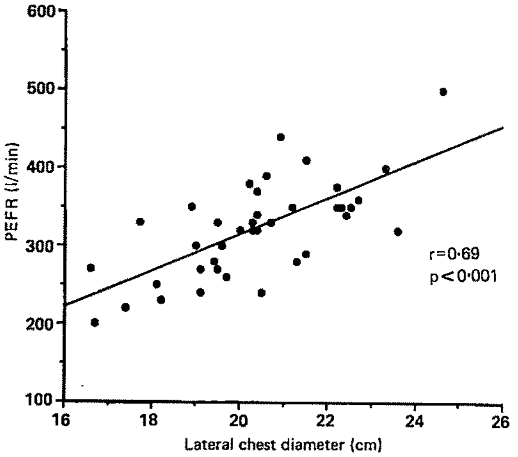

Figure 4 Association between PEFR and lateral chest diameter.

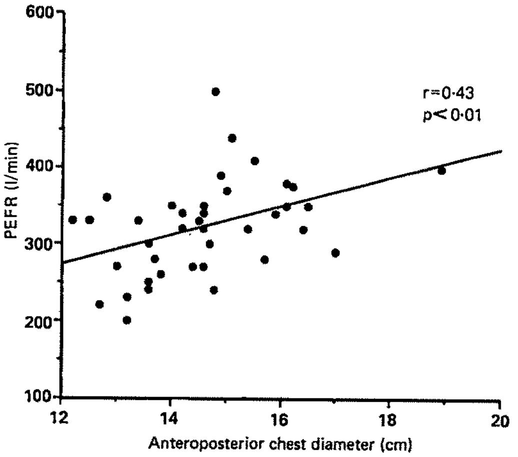

Figure 3 Association between PEFR and anteroposterior chest diameter.

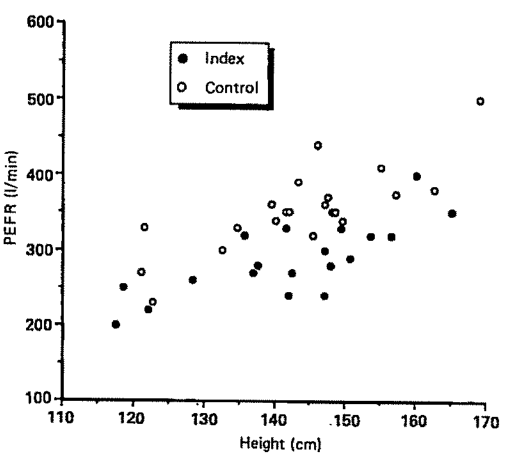

Figure 5 Association between PEFR and height in index and control children.

range 200–400 l/min) was significantly less than in controls (mean 355 (57), 230–500 l/min).

To ascertain whether PEFR showed progressive deterioration with the number or severity of episodes of acute chest syndrome, an analysis of covariance was conducted between PEFR, height, number of episodes of acute chest syndroe or severity of such episodes depicted as the number requiring hospital admission or transfusion treatment. The analysis showed no significant effect on PEFR of either the number or severity of episodes of acute chest syndrome.

Discussion

Recurrent respiratory infections were noted in the first case report of sickle cell disease[7] and the susceptibility of children with SS disease to serious pulmonary disease has since been well documented.[1,8] Abnormalities of lung volume and function have been reported in SS disease, although it is unclear the extent to which these changes reflect the abnormal chest shape of SS disease or histories of pulmonary complications. An earlier Jamaican study had shown that the diffusing capacity of the alveolar membrane was reduced in SS disease and was decreased further in patients with a history of pulmonary complications.[2]

The PEFR is a simple test of lung function amenable to population studies and domiciliary use. The Mini-Wright peak flow meter is cheap and provides a single reproducible measurement.[9] The major determinants of PEFR are the static recoil pressure of the lungs and airways resistance.[10] As the airways resistance in SS disease has been shown to be normal,[4,11] abnormal values for PEFR are likely to result from changes in lung compliance.

The only previous published study on PEFR in SS disease failed to show a difference between SS patients and normal controls,[5] but the study was small and only four out of 12 SS patients had had previous pulmonary complications (three with one episode and one with three episodes).

The present study has shown that when populations are selected according to an absence of acute pulmonary episodes or six or more episodes, highly significant differences in PEFR between the groups emerge. In children height appears to be a major determinant of PEFR,[6] but pairs were matched so that the mean difference between index cases and controls was only 0·9 cm. It was also possible that differences in chest dimensions or shape were associated with a proneness to acute pulmonary episodes and could have contributed to the difference in PEFR. However, analysis showed that there were no significant differences between index and control cases in anteroposterior or lateral diameters of the chest, chest circumference, or anteroposterior/lateral chest diameter ratio. All dimensions correlated significantly with PEFR, the closest correlation occurring with lateral chest diameter and circumference. There was no correlation between PEFR and anteroposterior/lateral chest diameter ratio. Furthermore as the ratio did not differ between index and control cases, this suggests that the abnormal chest shape in SS disease does not result from, or predispose to, multiple episodes of acute chest syndrome.

As these physical indices of chest shape or size did not differ between the study groups, one must conclude that chronic pulmonary changes consequent on the acute chest syndrome contribute to the observed differences in PEFR. The pathological mechanism of this reduced PEFR is conjectural but parenchymal scarring presumed to result from local infarction and alveolar necrosis has been observed at necropsy.[12] Such damage would be expected to be cumulative and to increase with each episode of acute chest syndrome, but there was no evidence of deteriorating PEFR with increasing episodes of six and above. It is still possible that cumulative damage would be demonstrable in patients with fewer episodes (one to five) or that the severity of the attack rather than the overall number of episodes is the major determinant of a reduced PEFR in these children.

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Varicella zoster virus DNA in throat swabs

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Abstract

Eighty one throat swabs from 18 patients infected with varicella were tested for varicella zoster virus DNA by the polymerase chain reaction. The positive rates were 26·2% (11/42) during the incubation period and 89·7% (35/39) after clinical onset. The results indicate the pharynx is a site for early replication of the virus.

Varicella, caused by primary infection with varicella zoster virus, is a common and highly contagious disease of childhood. The airway of patients infected with varicella is considered to be the main source of infection during the end of the incubation period and the first days of the rash. Isolation of the virus from the pharynx is usually difficult, however, and in a previous study we reported five isolates of the virus (4·3%) from 117 children with varicella by using human embryonic lung cell cultures.[1]

The polymerase chain reaction is a new technique that amplifies a specific sequence of DNA efficiently and is used for the detection of viral DNA in clinical specimens. Recently we established a method for detecting varicella zoster virus DNA by the polymerase chain reaction.[2] We report the results of our attempts to detect viral DNA in the pharynx of normal children with varicella infection by this technique.

Patients and methods

This study was conducted at the paediatric outpatient clinic of Showa Hospital over a six month period in 1989. When a child presented with varicella any siblings who had no history of varicella infection were asked to visit the clinic, and throat swabs were taken during the incubation period and after clinical onset of the infection. Eighteen normal siblings of children with varicella, who had no known underlying diseases and were not receiving immunosuppressive treatment, were included in this study; their ages ranged from 4 months to 8 years. The study was also performed on 16 healthy children as negative controls; their ages ranged from 5 months to 14 years of age. After the project was explained consent was obtained from the parents.

A total of 81 throat swabs were obtained from the 18 siblings of children with varicella. Forty two swabs were taken during the incubation period and 39 after appearance of the rash. Only one throat swab was taken from each of the 16 healthy control children. All swabs were placed in 3 ml of phosphate buffered saline and stored at −80°C before analysis.

The method used for detection of the viral DNA by the polymerase chain reaction has been described previously.[2] Four oligonucleotide pairs of 25 nucleotides (regions of thymidine kinase, thymidylate synthetase, glycoprotein I, and immediate early gene) were synthesised. The first three oligonucleotide pairs could be used as primers on the basis of specific DNA amplification. The amplification reaction was carried out in a DNA thermal cycler (Perkin-Elmer Cetus). The amplified product was detected by direct gel electrophoresis with ethidium bromide staining and by Southern blot hybridisation with a homologous ^{32}P-labelled cloned DNA probe (fig 1).

For determination of the sensitivity of the polymerase chain reaction in this system, a sample of cloned varicella zoster virus DNA (glycoprotein I region) was mixed with human placental DNA and this DNA was amplified with primers of glycoprotein I. The fragments of varicella zoster virus DNA with the same molecular weight as the expected DNA could be detected in agarose gel by ethidium bromide staining at a level of 5×10^3 copies, and 50 copies of the viral DNA could be detected by Southern blot hybridisation assay.

Results

Figure 2 shows the age and sex of the 18 children with varicella, maximum body temperature during the disease, and the results of the analysis by the polymerase chain reaction in throat swabs according to time of appearance of disease. In 11 of 42 (26·2%) throat swabs taken during the incubation period, varicella zoster virus DNA could be detected by the polymerase chain reaction with Southern blot hybridisation. We detected viral DNA in one swab 15 days before onset of the disease and in four of nine (44·4%) swabs during the incubation period

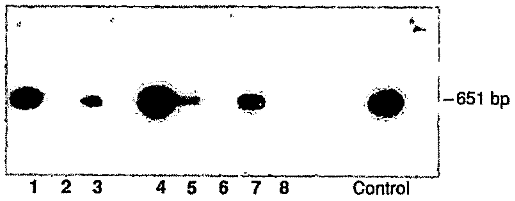

Figure 1 Autoradiograph after Southern blot hybridisation with ^{32}P-labelled probe for eight pharyngeal swabs and a positive control. Five samples (1, 3, 4, 5, and 7) contain varicella zoster virus DNA, bp=base pairs.

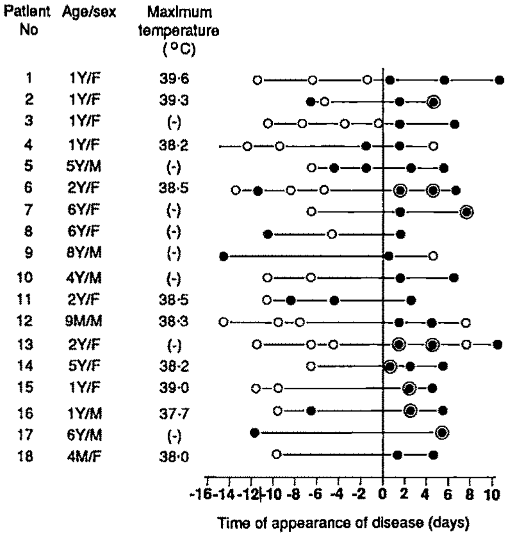

Figure 2 The results of the analysis by polymerase chain reaction in throat swabs according to time of appearance of disease. Not detected (open circle), detected (closed circle), and detected by direct gel electrophoresis (large open circle). Body temperature (−) was <37·5°C during the disease; Y=years, M=months.

within five days before the onset. The viral DNA could be detected in 35 of 39 (89·7%) throat swabs after appearance of the rash. The detection rate during the first three days after clinical onset of disease was 100% by the polymerase chain reaction with Southern blot hybridisation.

In 10 of 39 (25·6%) swabs after onset of disease, varicella zoster virus DNA was detected not only by Southern blot hybridisation but also by direct gel electrophoresis. On the other hand, no viral DNA could be detected in the swabs during the incubation period by the polymerase chain reaction with direct gel electrophoresis. In the throat swabs of the 16 healthy children no viral DNA was amplified specifically.

Discussion

In our previous studies we provided evidence for a mononuclear leucocyte associated viraemia occurring routinely during the incubation period and first few days of disease in nearly all normal children who had typical clinical manifestations of varicella.[3-6] However, isolation of varicella zoster virus from the pharyngeal area is usually difficult in normal children with varicella. It has been reported in a small number of cases after the onset and in no case during the incubation period by using the cell culture technique.[1 7]

The sensitive method that we established for detection of varicella zoster virus detected viral DNA between 15 days before and 11 days after appearance of the rash in normal children infected with varicella. The rate of detection during the incubation period was 25·6% (11/42), and within five days before onset of disease was 44·4% (4/9). After clinical onset of disease viral DNA could still be detected during the convalescent phase in two patients (1 and 13) and the rate of detection increased to 100% during the first three days of the rash. The findings were variable in four patients (2, 6, 8, and 13). We think that the difficulty in taking throat swabs from each child in a standardised fashion led to false negatives in a succession of positive findings. The rate of detection did not correlate with the maximum body temperature during the disease.

In a total of 10 swabs varicella zoster virus DNA was detected by direct gel electrophoresis, but these were swabs that were taken after clinical onset of the disease. The sensitivity of Southern blot hybridisation is higher than that by direct gel electrophoresis with ethidium bromide staining. From this point of view more viral DNA (in quantity) was found after clinical onset than during the incubation period.

The primary site of infection and replication of varicella zoster virus has been considered to be mucosa of the upper respiratory tract and/or conjunctivae. These results suggest that the pharynx is a site for early replication of the virus. Despite the fact that no virus could be isolated from the pharyx by cell culture technique, transmission of varicella zoster virus has been reported one to two days before onset of the rash. The results of this study might resolve the apparent paradox. By the use of the polymerase chain reaction we will be able to study further the pathology of varicella zoster virus infection.

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Staff training: a key factor in reducing intravascular catheter sepsis

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Abstract

A children's hospital nutritional care team prospectively monitored the frequency of sepsis in central venous catheters used for administering parenteral nutrition. During an initial study period of 12 months, 26/58 (45%) of catheters were removed because of proved sepsis. The possible causes of this alarmingly high rate were examined, with catheter care techniques on the wards coming under particular scrutiny. As a result protocols were modified and an intensive staff training programme implemented throughout the hospital, led by the nutritional care sister. Subsequently, the catheter sepsis rate was significantly reduced with only 9/107 (8%) of consecutive catheters becoming infected. These findings emphasise the key role that education of staff plays in controlling central venous catheter sepsis and the importance and cost effectiveness of special nursing staff in implementing such measures.

Central venous catheterisation provides reliable venous access during parenteral nutrition and permits the administration of hypertonic solutions. Catheter related sepsis remains an important unsolved problem[1 2] and results in significant morbidity and mortality. Infection control measures should include periodic prospective review of sepsis rates. In our hospital all parenteral nutrition is prescribed by a member of the nutritional care team[3]; this team also monitors complications related to nutritional support. Over a 12 month period (study 1) it became apparent that there had been a considerable increase in the rate of catheter sepsis above the 15% previously determined.[4] A number of different strategies for preventing sepsis have been proposed,[5] some of which have not been proved effective in practice.[6 7] The importance of impeccable catheter care, although difficult to define, is generally regarded as being crucial. We therefore determined to focus attention on existing central venous catheter care protocols and examine the way they were applied on the wards. This study describes our investigation of the epidemic, the ways in which we sought to improve matters, and the results of a planned education programme (study 2).

Subjects and methods

STUDY 1

Forty consecutive patients referred to the nutritional care team for parenteral feeding were included. Two thirds had undergone gastrointestinal surgery, most in the neonatal period. Cardiac surgery accounted for 20% and cardiac, oncology, and gastroenterology patients made up the rest. The median (range) age at starting parenteral feeding was 15 days (2 days–9 years).

A total of 58 central venous catheters were studied, comprising equal numbers of percutaneous Silastic[8] and Broviac catheters. Percutaneous catheters were inserted on the ward and a dry dressing applied to the skin entry site before taping in place with adhesive plaster. The skin entry site was not routinely inspected unless there were clinical suspicions of catheter sepsis, and dressings were not routinely changed unless soiled or loose. Broviac catheters were inserted under general anaesthesia in an operating theatre, usually by cutdown onto an internal jugular vein. A clear adhesive dressing (Opsite, Smith and Nephew) was then applied. All catheters were sited with their tip just within the right atrium.

Catheters were used exclusively for parenteral nutrition and not for administration of drugs or blood sampling. Parenteral feed source containers were changed every 24 hours and a 0·2 micron filter used in line with the amino acid/dextrose preparation. In the event of the catheter hub being disconnected (occlusion requiring flushing, or filter breakage), feed solutions were replaced with 10% dextrose until the next day's feed prescription became available.

A diagnosis of probable catheter sepsis was made in a feverish or unwell patient without evidence of focal infection such as otitis or pneumonia, and when urine culture was negative. Primary catheter sepsis was then considered to be proved when peripheral blood cultures were positive for bacterial pathogens. Treatment involved catheter removal and intravenous antibiotics, usually vancomycin and gentamicin, until sensitivities of organisms were available. Non-quantitative bacteriological techniques were used for blood cultures. Samples were placed in brain heart infusion broth (Oxoid UK Ltd) for aerobic culture, and thyoglycollate medium USP (Oxoid UK Ltd) for anaerobic culture. Broth bottles were incubated at 37°C and examined each day for evidence of growth. Positive cultures were subcultured to blood agar and examined by Gram film. All bottles were routinely subcultured at 48 hours and again after seven days' incubation. Fungal organisms were routinely sought.

Catheter tips were rolled across the surface of 5% blood agar plates, using the technique of Maki *et al*,[9] and were then incubated aerobically at 37°C. Using this method colony counts greater than 15 were considered additional evidence for catheter sepsis. The final diagnosis was based on positive blood cultures and clinical features, including symptomatic improvement after catheter removal. In four cases of catheter sepsis occurring in patients on long term parenteral feeding, antibiotic treatment was given with the catheter left in situ. In two instances blood cultures remained positive at 48 hours and the catheter was then removed, and on two occasions after 48 hours of treatment, blood cultures remained negative and antibiotics were successfully discontinued after two weeks with the catheter left in situ.

Education programme

Staff communication—After the analysis of the results in study 1, meetings were held between the nutritional care team and consultant microbiologist and staff from medical and surgical units. Routines for changing parenteral feed infusions and dealing with blocked lines were scrutinised by the microbiologist as they were being performed on the ward.

Hand washing—Forty per cent of medical and nursing staff were observed to follow an incomplete hand washing technique and efforts were directed at teaching correct hand washing procedure.[10]

Bag changes—After their usual practice of hand washing for two minutes in antiseptic soap (Hibiscrub), nurses were asked to start wearing sterile gloves. In addition to immersing the catheter hub in 70% isopropyl alcohol before disconnection, it was decided that the tubing up to 20 cm on either side of the catheter hub should also be cleaned with a gauze soaked in alcohol and then allowed to dry.

New guidelines for catheter care were drawn up,[11] emphasising the importance of aseptic technique, and the importance of minimising hub disconnections and line violations. It was agreed that two nurses rather than one should always be involved with changing parenteral nutrition feed bags so that one could handle only sterile equipment and the other 'dirty' equipment. This practice had lapsed under pressure of work on the ward where most parenterally fed patients were cared for, and only one nurse had been changing feeding bags.

Training—Given the high turnover of medical and nursing staff it was apparent that training programmes should recur at regular intervals so that new medical and nursing staff could be taught correct procedures. The need for junior medical staff to seek guidance from senior ward nurses on line care, for example when flushing a blocked central venous catheter, was emphasised and accepted.

A further series of meetings was arranged between medical and surgical teams and nutritional care sister to emphasise the importance of central venous catheter care, and arrangements made for this topic to be covered at each induction day for new medical and surgical staff. Practical demonstrations of line care and bag changing were organised for all nursing staff. Attendance was compulsory, and training carried out over a three month period. The nutritional care sister and clinical support nursing officer also arranged practical demonstrations of line care on all those wards regularly dealing with central lines. A video film showing bag changing and line flushing was also made by the department of medical illustration and the nutritional care sister and used in subsequent teaching sessions.

STUDY 2

After the intensive education programme, 92 patients were studied with a median age (range) at the start of parenteral feeding of 13 days (1 day–15 years). Seventy five (81%) patients were under 1 year of age and most (50, 54%) were recovering from gastrointestinal surgery; 24 (26%) had had cardiac surgery and the remaining patients had various different indications for nutritional support. In all, 107 central lines were inserted, and these comprised 35 triple lumen and 12 double lumen Vygon catheters, 34 percutaneous Silastic, and 26 Broviac catheters. Vygon catheters were inserted percutaneously either in theatre or on the intensive care unit and one channel devoted exclusively to administration of parenteral feeding solutions. Otherwise catheter insertion, dressing, and parenteral feeding protocols together with criteria for diagnosing sepsis were the same as in study 1.

STATISTICAL METHODS

Comparisons of the ages of patients at the start of parenteral nutrition and of catheter life was made using the Mann-Whitney U test. The incidence of catheter sepsis in each study was compared using the χ^2 test.

Results

STUDY 1 (BEFORE EDUCATION PROGRAMME)

The median (range) catheter life was 15 (3–66) days, giving a total of 963 catheter days in all. Thirteen of each type of catheter (26/58, 45%) became primarily infected, representing one episode of sepsis every 42 catheter days. Infections occurred sporadically after line insertion and no significant difference was found comparing the duration of catheter life in infected and non-infected catheters ($p=0·64$). In 23 cases, coagulase negative staphylococci were isolated from blood and/or line, with *Staphylococcus aureus* being found in two cases and *Escherichia coli* in one.

STUDY 2 (AFTER EDUCATION PROGRAMME)

The median (range) catheter life was 10 (1–84) days giving a total of 1684 catheter days in all. Now, only 9/107 (8%) of catheters became primarily infected (five percutaneous Silastic, three Vygon, one Broviac), a significantly lower number than before the education programme ($p<0·001$) representing one episode of sepsis/189 days of catheter use. Again, infections occurred sporadically after catheter insertion and the life of infected catheters was not significantly greater than that of non-infected catheters ($p=0·17$). *E coli* was isolated from four cases of catheter sepsis, coagulase negative staphylococci from three, and *Klebsiella aerogenes* and *Streptococcus viridans* from the remaining two.

There was no significant difference found when comparing the age of patients at the start of parenteral feeding in each group (p=0·24) but catheter life was significantly shorter in the patients in study 2 (p=0·01).

Discussion

The first part of this study showed that catheter sepsis rates among parenterally fed patients had increased from 15% to 45%, after a period when catheter infection had not been closely monitored. An intensive programme of staff education was then initiated, which emphasised the importance of scrupulous aseptic technique and led to several changes in catheter care protocols. We cannot, of course, be sure about the precise mechanisms by which our education programme brought about such a dramatic reduction in catheter sepsis rates from 45% to 8% (see table). Perhaps the most important of these was the requirement that two people should be involved with each central venous catheter disconnection and feed bag change. Although this had previously been our recommendation, the practice had lapsed during a period when increasing numbers of patients were cared for by fewer nursing staff.

The reduction in catheter sepsis after implementation of the education programme could not be accounted for by other factors. The age of patients and clinical indications for feeding were much the same in each part of the study. Although the length of time for which catheters were in situ was significantly greater in study 1, in neither study was there a simple association between days in situ and risk of infection. Sepsis occurred sporadically after insertion, and no significant difference was found comparing catheter life in non-infected and infected catheters. Although Vygon percutaneous catheters were used during study 2, the reduction in catheter sepsis remains unchanged even if these are excluded from the analysis.

In controlling complications of parenteral nutrition, particularly catheter related sepsis, the key role of specially trained nursing staff,[7 12] often in the context of a nutritional care team,[13] has gained widespread recognition, together with the appreciation that they are cost effective. Based on the assumption that patients who develop catheter sepsis probably stay on average a week longer in hospital than they would otherwise have done, the cost saving brought about by our intervention study through a reduction in infection over the next year would have been approximately £80 000 (£870·00 per parenterally fed patient). This takes into account the cost of antibiotic treatment and mean cost of one week's inpatient care.

Factors which may help reduce central venous catheter sepsis

Prospective audit	Warns of adverse trends Raises staff awareness
Catheter use	Dedicated to parenteral feeding Minimal line violation
Bag changes	Two nurse system Sterile gloves Attention to hub and adjacent tubing
Training	Recurrent staff training programme Ward demonstrations Video film Central role of nutritional care nurse

Infecting organisms come primarily from the catheter hub,[14–16] and studies which have concentrated on minimising the risk of bacterial hub contamination have shown significant reductions in sepsis rate.[17] Catheter infection by organisms gaining access to the bloodstream from the skin entry site is relatively uncommon; this explains why attempts to reduce sepsis rates by topical application of antibiotic and antiseptic agents,[6] or by bringing the catheter out through a skin tunnel,[18] have not been shown to be effective.

Prevention of central venous catheter sepsis is particularly difficult in infants, who often have skin contaminated with faeces, and who tend to play with or chew on catheters and connections. There is a natural reluctance on the part of many units to publish figures showing a high catheter sepsis rate, although some have reported experiences similar to our own.[19 20] We suspect that even collection of such data is not routine in many centres and yet our study, the first of its kind in children, emphasises how infection rates can suddenly increase. Careful prospective monitoring of catheter sepsis is essential if adverse trends are to be reliably identified at an early stage and then reversed.

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Evaluation of light microscopy to localise the site of haematuria

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Abstract

Red cell morphology was examined by light microscopy in 122 urine specimens from 99 patients with haematuria in an attempt to define the site of origin. Altogether 84% of glomerular bleeding and 91% of non-glomerular bleeding was correctly assigned according to diagnoses determined by renal biopsy in 51 patients and clinically in 48. The test should be interpreted with caution as both false positive and false negative results were observed, some in the same individual with unchanged pathology at different times. No advantage of phase contrast over bright field microscopy was apparent even when examining uncentrifuged urines.

The observation of Birch and Fairley that red cell morphology could be used to localise the site of haematuria in the urinary tract[1 2] has been confirmed by a number of other groups.[3–6] All used phase contrast microscopy; this is, however, frequently unavailable and therefore limits the usefulness of this otherwise simple and inexpensive test. Another problem associated with the technique is high interobserver variation due mainly to confusion in distinguishing normal and abnormal cell types.[7] Birch and Fairley classified crenated cells as normal and anisocytosis and bizarre deformed cells as diagnostic of glomerular bleeding. Fassett *et al* considered cells with surface projections (echinocytes) as abnormal,[8] but Bessis and Mohandas have shown that echinocytes and stomatocytes are normal variants as they regain normal morphology after adjustment of pH and ionic strength.[9] We have recently observed that low osmolality (<300 mmol/kg) can preferentially reduce deformed cell counts (unpublished observations). The morphological pattern may also vary in the same patient at different times.[10]

In the present study we have evaluated the use of routine bright field rather than phase contrast microscopy in prediction of the site of bleeding in the urinary tract, and further assessed the reliability of the test, using the morphological criteria of Birch and Fairley.

Methods

One hundred and twenty two spot mid-stream urine specimens, all at least 1+ blood on dipstick testing (BM Test 5L, Boehringer Manheim) and with red cell count greater than 20×10^6/l, were collected from 99 patients. Diagnostic details are given in table 1. Multiple samples (two to five specimens collected at least 24 hours apart—usually one week) were obtained from 16 of the patients in order to assess the within patient variability of the method. Altogether 100 samples were from patients with glomerular disease and 22 from patients with lower tract disease. Red cells were counted using a Neubauer chamber, and morphological studies performed 'blind' at ×450 magnification using uncentrifuged specimens within one hour of collection. The first 20 specimens were examined with both phase contrast and bright field microscopes and no differences in interpretation were apparent. Subsequent work used bright field microscopy only. Eighty per cent dysmorphic cells was taken to indicate unequivocal glomerular bleeding, 20–80% dysmorphic cells as a mixed picture, and less than 20% as non-glomerular bleeding.[2–4]

Casts were counted in the sediments from 10 ml aliquots of the urine specimens, centrifuged for five minutes at 540 *g* and resuspended in 0·2 ml supernatant urine. Only red cell, cellular, and granular casts were analysed. Proteinuria was assessed by dipstick testing (BM Test 5L test strips).

Results

The localisation of bleeding inferred from morphological studies of red cells is compared with conventional diagnosis in table 2.

An unequivocal glomerular pattern ($>80\%$ dysmorphic red cells) was found in 60/100 samples from patients with glomerular disease. A further 26 samples from patients with glomerulopathies showed a mixed picture. Fourteen specimens from 13 patients with glomerular disease, 10 proved at biopsy, had less than 20% of deformed red cells in their urine and would thus have been misclassified. Two of 22 samples from patients with lower tract bleeding had high proportions of deformed red cells, one greater than 80%, the other a mixed pattern with 71% deformed cells.

The effect of cell number on the reliability of the test is also shown in table 2. There was no difference in the diagnostic sensitivity between samples with 20–50 cells$\times10^6$/l, 51–100 cells$\times10^6$/l, or more than 100 cells$\times10^6$/l for the diagnosis of glomerular bleeding. However both the samples giving inappropriate patterns from lower tract bleeding had low cell counts (30 and 50 cells$\times10^6$/l). In our series of samples the sensitivity of the technique, taking mixed pictures as diagnostic of glomerular bleeding, was 86–87% with a specificity of 91%. The predictive value of the test was 98% for glomerular

Table 1 Patients and diagnoses

Disease	*Total No patients*	*No of patients biopsied*	*No of clinical diagnoses*	*Total No samples*
Glomerular				
Acute post-streptococcal glomerulonephritis	1	1		2
Alport's syndrome	19	5	14	22
Chronic glomerulonephritis	1		1	1
Diffuse mesangeal sclerosis	1	1		1
Transplant rejection	2	2		2
Focal glomerulonephritis	1	1		1
Focal segmental glomerulosclerosis	1	1		4
Henoch-Schönlein purpura	9	6	3	13
Haemolytic uraemic syndrome	2		2	2
IgA nephropathy	10	10		13
Loin pain haematuria	1	1		1
Mesangiocapillary glomerulonephritis	5	5		8
Mesangeal proliferative glomerulonephritis	2	2		2
Minimal change nephrotic syndrome	2		2	2
Membranous nephropathy	2	2		3
Polyarteritis nodosa	2	2		3
Reflux nephropathy	7	1	6	7
Sickle cell trait	1	1		1
Systemic lupus erythematosus	7	7		11
Thin membrane disease	1	1		1
Subtotal	77	49	28	100
Non-glomerular				
Adult polycystic kidney disease	3		3	3
Calculi	2		2	2
Bladder carcinoma	1	1		1
Interstitial nephritis	1	1		1
After renal biopsy	2		2	2
Postoperative	8		8	8
Trauma	1		1	1
Urinary tract infection	3		3	3
Vulvovaginitis	1		1	1
Subtotal	22	2	20	22

Table 2 Comparisons of diagnosis with urinary red cell morphology. Results are number (%)

Cells×10⁶/l	*No of samples*	*Microscopic picture*		
		Glomerular	*Mixed*	*Non-glomerular*
Glomerular disease:				
21–50	16	9 (56)	4 (25)	3 (19)
51–100	13	7 (54)	5 (39)	1 (8)
>100	71	44 (62)	17 (24)	10 (14)
All samples	100	60 (60)	26 (26)	14 (14)
Non-glomerular disease:				
21–50	3	1 (33)	1 (33)	1 (33)
51–100	2			2 (100)
>100	17			17 (100)
All samples	22	1 (5)	1 (5)	20 (91)

Table 3 Microscopic picture in multiple samples from individual patients

Diagnosis	*Microscopic picture (% dysmorphic cells)*
Henoch-Schönlein purpura	>80, >80, >80, 20–80, 20–80
Henoch-Schönlein purpura	>80, 20–80
Henoch-Schönlein purpura	>80, >80
Alport's syndrome	>80, >80
Alport's syndrome*	20–80, <20
Alport's syndrome	>80, >80
Mesangiocapillary glomerulonephritis*	>80, >80
Mesangiocapillary glomerulonephritis*	>80, >80, 20–80
Mesangiocapillary glomerulonephritis*	>80, 20–80, 20–80
Systemic lupus erythematosus*	<20, <20
Systemic lupus erythematosus*	>80, >80, 20–80, <20
IgA nephropathy*	>80, >80
Membranous nephropathy*	<20, <20
Polyarteritis nodosa*	20–80, <20
Focal segmental glomerulosclerosis*	>80, 20–80, <20
Acute post-streptococcal glomerulonephritis*	20–80, 20–80, <20

*Proved at biopsy.

bleeding and 59% for lower tract bleeding, rising to 100% and 63% respectively for cell counts greater than 50×10^6/l. Within patient variation is shown in table 3. All patients had glomerular disease. Five of 16 showed an unequivocal glomerular pattern on both occasions studied, and 2/16 were incorrectly assigned on both occasions. One of these latter patients had bacteriuria and other evidence of urinary tract infection which may account for the erroneous results. Three of 16 patients gave mixed pictures and lower tract pictures at different times and 2/16 a combination of all three pictures. We could discern no association between the pattern of haematuria and the course of the disease.

Casts (38 red cell, nine renal tubular cell, pus cell or coarse granular casts) were present in 47 samples, all from patients with glomerular disease. In 10 of these (nine with glomerulopathies proved at biopsy and one with Alport's syndrome) a mixed morphological picture had been observed; three had shown a lower tract pattern. There was a significant correlation between red cell number and casts ($r=0{\cdot}56$, $p<0{\cdot}001$).

Proteinuria did not correlate with red cell morphology in our study. Altogether 19/22 samples from patients with lower tract bleeding had 1+ or greater (>0·3 g/l) protein on dipstick testing and 24/100 samples from patients with glomerular haematuria were protein negative.

Discussion

It has been claimed that the site of bleeding in haematuria can be assessed with high sensitivity and specificity (>95%) by analysis of red cell morphology using phase contrast microscopy.[1–6] Rizzoni has stated that the standard microscope is equally reliable.[11] We found no difference at all between phase contrast and bright field microscopy, but found red cell morphology gave misleading results in 40% of glomerular (26% mixed picture, 14% non-glomerular type pattern) and 9% of non-glomerular cases. Urinary tract infection interfered with the interpretation of red cell morphology in at least one of our patients. It is possible that our use of uncentrifuged specimens affected the reliability of the test as a number of workers claiming higher sensitivities used centrifuged specimens. However, Venkatraman *et al* compared centrifuged and uncentrifuged specimens and found little difference.[7]

In our study 26/27 samples with mixed red cell patterns came from patients with glomerular bleeding, seven of these also had pathological casts. We therefore agree with Rizzoni *et al* that mixed pictures are predominantly glomerular.[5] If these criteria are accepted the sensitivity of localisation of haematuria in the present study is 86% for glomerular (98% predictive value) and 91% for non-glomerular bleeding (63% predictive value). Our conclusions are therefore that the study of red cell morphology in the urine of patients with haematuria can be a useful guide to the site of bleeding, but should be combined with other tests as there are a number of patients in whose samples the pattern is inappropriate or equivocal. Very dilute samples or samples from patients with bacteriuria may be misleading. Mixed pictures imply glomerular origin. The degree of haematuria does not affect the result provided the red cell count is above 50 cells$\times 10^6$/l. Reliability is not compromised if uncentrifuged urine is inspected using bright field rather than phase contrast microscopy, making the test particularly simple, rapid, and inexpensive.

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More on cytokines

I referred recently to the possible role of cytokines in meningitis.[1] Now workers in the Gambia (Kwiatkowski *et al. Lancet* 1990; **336**: 1201–4) have studied plasma concentrations of cytokines in children with malaria. Concentrations of tumour necrosis factor on the first day of illness in children with non-cerebral malaria were about twice those of children with other illnesses. In those who had cerebral malaria but survived the increase was five-fold but in those who died of cerebral malaria concentrations were increased by a factor of 25 or more. With antimalarial treatment the concentrations fell in the survivors but not in those who eventually died. Similar but much less pronounced changes were seen in plasma concentrations of interleukin 1 alpha.

Whether the increase in circulating cytokines is simply a reflection of the severity of the disease process or part of the pathogenesis of cerebral malaria is as yet uncertain. Presumably, as in meningitis, the next step will be a trial of steroid or other drugs which inhibit cytokine release.

ARCHIVIST

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Tolerance to somatostatin analogue in a preterm infant with islet cell dysregulation syndrome

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Abstract

An infant of 31 weeks' gestation presented with refractory neonatal hypoglycaemia secondary to islet cell dysregulation. Treatment was started with somatostatin analogue and his glycaemic control improved initially. Tolerance developed, however, in that the dose required to maintain control increased by a factor of 40. The infant subsequently underwent pancreatectomy. It is safe to use somatostatin analogue in a preterm infant, but tolerance to the drug rapidly develops.

Somatostatin is being used increasingly to manage refractory hypoglycaemia caused by hyperinsulinism, usually as a short term treatment before pancreatectomy. In this report we describe the presentation of severe refractory hyperinsulinaemic hypoglycaemia secondary to islet cell dysregulation in a preterm infant, and the difficulties that we encountered when we treated him with somatostatin analogue.

Case report

The male infant of a 26 year old, single primigravida mother was born after spontaneous onset of labour and normal vaginal delivery at 31 weeks' gestation (judged by mother's dates and by ultrasonography). Episodes of fetal bradycardia were recorded during labour and there was evidence of retroplacental haemorrhage after delivery of the placenta. At birth the infant was hypotonic and bradycardic and required resuscitation with intermittent positive pressure ventilation for six minutes. The birth weight was 2490 g and the head circumference was 31 cm (both measurements above the 90th centile). There were no abnormal features, genitalia were normal, and the infant was not pigmented.

He was electively intubated and ventilated at 5 hours of age, and ventilation was continued apart from a brief, unsuccessful, trial of extubation at 30 hours.

At 1 hour of age laboratory blood glucose measurement was <0·5 mmol/l before starting an intravenous infusion of dextrose 4 mg glucose/kg/minute. Hypoglycaemia persisted despite the rate of infusion being increased to 16 mg glucose/kg/minute a number of bolus doses of 10% dextrose being given. On day 3 he had generalised and focal convulsions, which were treated with phenobarbitone.

At 57 hours of age he was transferred to the regional neonatal unit. Biochemistry confirmed hyperinsulinaemic hypoglycaemia with total blood ketone body concentration of 0·02 mmol/l, non-esterified fatty acid concentration of 0·005 mmol/l, and insulin concentration of 44·7 mU/l while hypoglycaemic. Cortisol and growth hormone concentrations on the first day of life were 1228 nmol/l and 17·3 μU/l, respectively. A central venous line was inserted so that hypertonic glucose solutions could be given and continuous nasogastric feeds were started. Subsequently the total energy intake that was required to prevent hypoglycaemia rose to a maximum of 1·59 MJ (380 kcal)/kg/day, which was given as 20% dextrose intravenously and Prematalac supplemented with Caloreen through the nasogastric tube. Glucagon given intramuscularly resulted in a transient glycaemic response, which supported the diagnosis of hyperinsulinism. Diazoxide and chlorothiazide given orally also had temporary glycaemic effects.

On day 10, treatment with somatostatin analogue (Sandostatin, Sandoz) was started, initially as boluses of 2·5 μg given subcutaneously every four hours. The biochemical response to the first dose is shown in the table. After this favourable initial response, progressively larger bolus doses were required to maintain normoglycaemia and a subcutaneous infusion was

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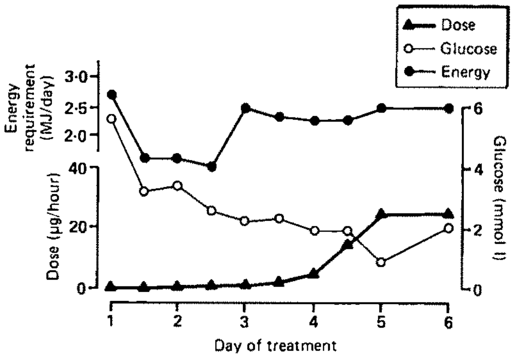
Biochemical response to 2·5 μg Sandostatin given subcutaneously

	Time after injection (hours)					
	0	*1*	*2*	*3*	*4*	*5*
Glucose*	1·50	7·80	—	5·94	4·26	4·20
Pyruvate*	0·07	0·06	0·08	0·09	0·08	0·08
β hydroxybutyrate*	0·01	0·01	0·01	0·01	0·01	0·01
Acetoacetate*	0·05	0·04	0·05	0·04	0·06	0·04
Glycerol*	0·28	0·22	0·25	0·27	0·28	0·26
Alanine*	0·30	0·27	0·36	0·37	0·39	0·38
Lactate*	1·55	1·12	1·40	2·39	2·31	2·06
Non-esterified fatty acid*	0·10	0·09	0·11	0·09	0·08	0·18
Insulin (mU/l)	37·4	6·3	10·4	15·3	13·1	19·2

*All concentrations are mmol/l.



Dose of Sandostatin, blood glucose concentration, and energy requirement during treatment.

begun. Hypoglycaemia and the need for a high energy intake persisted, however, despite increasing the dose to 25 µg/hour (figure).

During this period he developed heart failure secondary to fluid overload, ventilatory requirements remained high with radiographic appearances of respiratory distress syndrome, and the infant remained irritable. Cerebral ultrasonography showed increased echogenicity in both hemispheres, and there were multifocal discharges on electroencephalography.

As the hypoglycaemia was proving to be refractory to medical treatment, a 99% pancreatectomy was performed under general anaesthesia on day 15. Histological examination confirmed the appearances of 'nesidioblastosis', with disorganisation of islet architecture and the presence of insulin secreting cells in the duct epithelium of the exocrine pancreas. Sandostatin infusion was discontinued at induction of anaesthesia and hydrocortisone was given because of the suppressive effect of Sandostatin on adrenocorticotrophic hormone secretion. After operation, he was hypoglycaemic and then hyperglycaemic, but subsequently there was progressive reduction in the intravenous glucose intake to 7 mg glucose/kg/minute, and full nasogastric feeding was established on the seventh postoperative day. Insulin was not required.

The clinical improvement was confirmed by the biochemical findings (glucose concentration 8·7 mmol/l, total ketone bodies 0·10 mmol/l, glycerol 0·31 mmol/l, and insulin <1·0 mU/l). There was no clinical or biochemical evidence that Sandostatin had had any adverse endocrinological effects, cortisol concentrations during and four weeks after treatment were 189 nmol/l and 205 nmol/l, respectively, and thyroid function tests during treatment were within normal neonatal ranges (thyroxine 97 nmol/l, triiodothyronine uptake 32%, and free thyroxine index 31%). The baby was extubated into air on the fourth postoperative day.

He was discharged home at the age of 6 weeks (37 weeks corrected age), and bottle fed with a proprietary formula supplemented with pancreatic enzymes. Strict blood glucose monitoring has been carried out by his parents and, though he has had no episodes of symptomatic hypoglycaemia, home monitoring has shown a steady trend towards low blood glucose measurements despite his now being on a normal weaning diet. Since the age of 5 months diazoxide 20 mg/kg/day and chlorothiazide 10 mg/kg/day have been required to maintain blood glucose concentrations between 2 and 4 mmol/l. The baby's weight was on the 25th centile at the time of writing and his head circumference was growing parallel to and just below the 50th centile. His developmental progress is appropriate for corrected gestational age, and he is a pleasant baby, though somewhat difficult to feed at times.

Discussion

Others authors have described the use of somatostatin in the control of neonatal hypoglycaemia secondary to the dysregulation syndromes of the endocrine pancreas, including 'nesidioblastosis' and β cell adenoma.[1 2] Similar doses to those that we describe have led to a prompt rise in blood glucose concentrations accompanied by a fall in plasma insulin. Aynsley-Green *et al* also described an increase in blood ketone bodies and glycerol after somatostatin infusion.[3] The use of somatostatin is, however, limited by the need for continuous infusions, with hypoglycaemia developing rapidly as soon as the infusion is stopped. There is also concern about the effects of somatostatin on growth hormone, thyroid hormones, corticosteroids, and gut hormones in such young infants.[3] Glucagon secretion is also suppressed during treatment, which may explain the disappointing results sometimes obtained.[1 3] For this reason, it has been recommended that glucagon should be given concurrently with somatostatin.[4 5] More recently the use of somatostatin analogue in the management of neonatal hypoglycaemia has been described. It is possible to give intermittent doses, as the analogue has a long half life, and it is claimed that despite suppression of growth hormone, long term treatment does not result in failure of growth.[6 7]

This case is unusual on two counts: the presentation of severe hyperinsulinism secondary to an anatomical abnormality of the pancreas in a very preterm infant, and the rapid development of tolerance to Sandostatin. Undoubtedly the management of severe hypoglycaemia was made more difficult by the other problems of prematurity, namely respiratory distress syndrome and respiratory failure. This prevented early establishment of high energy enteral feeds, and left the infant totally dependent on parenteral glucose to maintain substrate availability.

The tolerance to somatostatin analogue that developed was so dramatic (a 40-fold increase in dose in three days) that it almost amounted to a failure of treatment. It allowed no reduction in energy intake, and barely maintained normoglycaemia. Such a phenomenon has not to our knowledge previously been reported, and was surprising in this case in view of the good response to the first dose.

Somatostatin is a potent inhibitor of endocrine secretion and may be expected to have widespread effects. Of particular concern in the preterm neonate are effects on gut motility and thyroid function. No deleterious effects were observed on gut function, however, and thyroid function tests remained normal, as might be expected from the long half life of thyroxine. The plasma cortisol concentration must be interpreted with caution, as the presence of an apparently normal concentration cannot be taken to predict an appropriate stress response.[8] It was for this reason that steroids were given during the operation.

We recommend that, with appropriate monitoring of the metabolic and endocrine state, somatostatin analogue can be used in the short term management of hyperinsulinaemic hypoglycaemia secondary to islet cell dysregulation. In view of the tolerance to the drug that developed, however, it is unlikely that its use will obviate the need for a definitive operation.

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Ureteric sludge syndrome

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Abstract
Four cases of a form of obstructive uropathy previously unreported in children are described. All presented with oligoanuria and either flank pain or fluid retention and had evidence of crystalline sludge in their lower ureters. Three cases had an underlying crystalluria.

Currently children who present with oligoanuria after acute dehydrating or diarrhoeal illnesses are invariably assumed to have either prerenal azotaemia, acute tubular necrosis, haemolytic uraemic syndrome, or obstruction to drainage from a single kidney as might occur with calculus or ureterocoele. We present four cases of a form of obstructive uropathy, which may commonly be overlooked or misdiagnosed as one of the above conditions.

Case reports

CASE 1

A 13 year old boy presented in 1978 with acute abdominal pain, haematuria, and profuse uric acid crystalluria. His father had a history of urinary calculi, and his mother had recurrent abdominal pain associated with haematuria. On examination he was of normal stature with no renal enlargement or tenderness and his blood pressure was 120/80 mm Hg.

Serum creatinine concentration was 70 µmol/l and uric acid 0·33 mmol/l. An intravenous urogram showed normal renal size and contour with good excretion bilaterally. A 24 hour urine sample confirmed an increased uric acid excretion of 4·4 mmol/day (normal being less than 3·5).

After discharge he remained well apart from non-specific abdominal pain. He represented four months later in acute renal failure. On admission he appeared uraemic and was mildly dehydrated. His blood pressure was 130/100 mm Hg. The rest of the examination was normal. Serum creatinine was now 1550 µmol/l with serum uric acid of 1·7 mmol/l. Haemoglobin concentration was 143 g/l; platelet count and blood film were both normal.

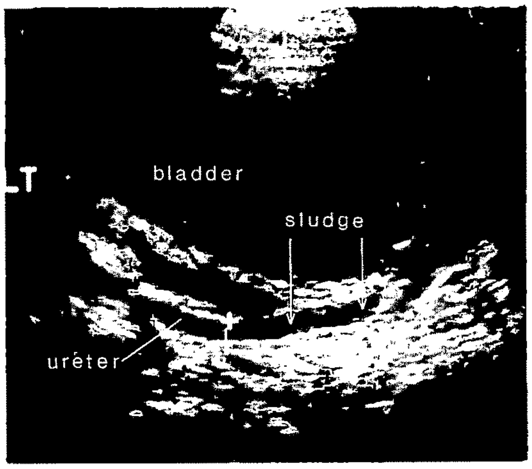
A presumptive diagnosis of acute urate nephropathy was made, and allopurinol started intravenously. After two haemodialyses he remained anuric and retrograde ureteric catheters were inserted. Crystalline sludge was noted at the base of the bladder, and urine samples from each ureter had high concentrations of uric acid. Both renal pelvices were washed out with an 8·4% solution of sodium bicarbonate. After this procedure there was a prompt diuresis of two litres of urine over the next hour. Without further dialysis renal function returned to normal.

CASE 2

In 1988 a 3 year old girl presented to a peripheral hospital over 1200 km north of Perth with a four day history of vomiting and diarrhoea. Urinalysis had shown large amounts of blood. Her condition deteriorated and she stopped passing urine. She developed a raised blood pressure to a maximum of 130/110 mm Hg with a rising serum creatinine concentration. A diagnosis of acute renal failure secondary to dehydration was made, and she was transferred by Royal Flying Doctor Service to our hospital. On admission she was unwell with facial oedema and raised blood pressure. Serum creatinine was 300 µmol/l and a full blood count was normal. Renal ultrasound showed swollen echogenic kidneys with dilated collecting systems and crystalline sludge (see figure). Twelve hours after admission she underwent a spontaneous diuresis and the ultrasound appearances had largely resolved by the next day. Urinalysis was not performed before discharge and therefore the nature of the sludge is not known. Because of the distance involved follow up was not possible.

CASE 3

A 14 month old boy presented in 1986 with a six day history of vomiting and diarrhoea. His urine output had been poor for 36 hours before admission. When initially seen he was 5%



A renal ultrasound scan showing dilatation of the left ureter. The picture shows debris in the distal end of the ureter (between the arrows) consistent with crystalline sludge. Note the absence of calculi and anatomical obstruction.

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dehydrated, his abdomen was soft and non-tender, and a small sample of urine was heavily bloodstained. As he was refusing to drink, fluids were given initially by nasogastric tube; however, as he failed to improve and did not produce urine for over 48 hours intravenous hydration was started on day three. He quickly developed periorbital and scrotal oedema with a raised blood pressure of 180/100 mm Hg. Serum creatinine was 245 μmol/l. Haemoglobin, blood film, and platelet count were normal. Renal ultrasound showed normal renal parenchyma, dilated collecting systems, and an empty bladder. The dilatation appeared acute with no evidence of caliceal clubbing. The likely diagnosis was considered to be vesicoureteric junction obstruction secondary to crystal sludge.

He remained irritable with a raised blood pressure for 24 hours, despite several doses of hydralazine and frusemide intravenously. A spontaneous diuresis occurred on day four with an improvement in his condition and a return to normal blood pressure. Repeat ultrasound one month after discharge showed a normal collecting system on the right and mild dilatation on the left. There was no debris evident. A micturating cystourethrogram showed no abnormality.

Subsequent studies on the child showed a raised cystine excretion at 195 mmol/l suggesting heterozygous cystinuria. Both his parents also had cystinuria in the heterozygous range.

CASE 4

A 13 year old boy, who received regular transfusions for β thalassaemia, presented in 1981; he was unwell with a fever of 39·5°C, sore throat, and cough. He was thought to have a viral illness, was treated symptomatically, and his regular blood transfusion was delayed.

He deteriorated progressively with increasing abdominal pain, vomiting, and diarrhoea and was readmitted three days later. At this stage he was passing only a few drops of heavily bloodstained urine. He was mildly dehydrated and afebrile, with loin tenderness on the left side. His haemoglobin was 86 g/l, white cell count $13{\cdot}0\times10^9$/l with a normal differential. Blood film and platelet count were normal. Serum creatinine concentration was 395 μmol/l and uric acid 0·11 mmol/l. Urine and blood cultures taken at that time later proved to be sterile.

His urine output remained poor, and on the fourth day he underwent bilateral renal exploration and insertion of nephrostomy drainage tubes. At operation the right kidney was swollen, discoloured, and oedematous; old blood clot was washed from the ureter. The findings on the left side were similar but less noticeable; urine, but no clot, was found under some pressure in the pelvis. Urine output improved and renal function returned to normal after irrigation.

Subsquent studies showed that his uric acid excretion was abnormally high while on desferrioxamine with an excretion of 9 mmol/day. This fell to within the normal range when this treatment was discontinued.

Discussion

All the children described exhibit features one would expect in an obstructive uropathy—namely, bilateral dilatation of the ureters associated with impaired renal function, prompt diuresis, and return of outflow tract calibre to normal once the obstruction is relieved. We demonstrated blood or crystalline sludge in dilated lower ureters. There was no evidence of stones, uterocoeles, or other obstructive elements.

Evidence that crystalline sludge was the cause of the obstruction is clear from the first two cases as it was seen directly on cystoscopy in the former and on ultrasound in the latter. The presence of sludge is strongly implied in the latter two cases, and they both demonstrated raised excretion of either cystine or uric acid. The boy with thalassaemia had gross haematuria and blood clots were found at operation. Though it is possible that the clot was the primary cause of the obstruction, it must be exceedingly rare for gross haematuria to cause a bilateral ureteric obstruction. It would be reasonable to suggest that the bleeding and renal oedema were secondary to the obstruction that had been present for at least four days before surgery.

Predisposing factors that we have identified as a cause of the syndrome are firstly dehydration, which in all of our cases followed either a febrile or diarrhoeal illness, and secondly an underlying crystalluria, which was demonstrated in three out of four cases. Two had a raised excretion of uric acid and one of cystine.

Tubular obstruction due to crystalluria has previously been described with sulphonamides,[1] ethylene glycol poisoning, primary hyperoxaluria,[2] and uric acid nephropathy complicating the treatment of leukaemia and lymphomas.[3] Our first case was initially thought to have uric acid nephropathy; however, the failure to respond to dialysis and the prompt recovery after retrograde irrigation makes this diagnosis unlikely. To the best of our knowledge ureteric obstruction due to crystalluria has not previously been reported in children. It has been mentioned briefly in one adult textbook but no details were given.[4]

This is an important condition to recognise as failure to do so could lead to acute renal failure or severe hypertension as occurred in cases 1 and 3 respectively. The diagnosis should be considered when a child presents with dehydration and oligoanuria, particularly when there is failure to respond to adequate volume replacement. Ultrasound examination of the vesicoureteric junction is likely to assist the diagnosis. It has been established previously that ultrasound is a highly effective method of screening for obstructive causes of renal failure[5] and in evaluating renal colic.[6] In our series cases 1 and 4 did not have renal ultrasound examinations as this facility was not available at our hospital until 1982. In cases 2 and 3 however, this procedure made a significant contribution to the diagnosis.

Treatment should initially consist of intravenous fluid boluses and diuretics. Although two of our children had spontaneous diuresis, the other two required surgical decompression with either an antegrade or retrograde ureteric irrigation. We would therefore advise that failure to respond to conservative management within 24 hours, or the development of hypertension, should lead to more direct attempts to relieve obstruction.

Finally we recommended that after recovery, all of these children should be investigated for the possibility of an underlying crystalluria.

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Pain and measles, mumps, and rubella vaccination

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Abstract
Seventy seven children (mean age 44·2 months) were entered in a randomised double blind study to find out if two commonly used measles, mumps, and rubella (MMR) vaccines (Pluserix and MMR II) caused pain on injection. Pain was judged by the amount of crying. Infants given MMR II were 2·31 times more likely to cry than those given Pluserix.

A vaccination programme to eliminate measles, mumps, and rubella (MMR) from the British Isles was introduced in October 1988. Two vaccines, Pluserix (Smith Kline French) and MMR II (Wellcome), have been used extensively in the campaign and they have comparable immunogenicity and reactogenicity.[1] Since the start of the campaign some family doctors in Ireland reported that the MMR II vaccine caused more distress to children than the Pluserix vaccine. Similar reports came from the United Kingdom.[2] Although the data sheet for MMR II states that the vaccine may cause burning or stinging at the injection site for a short time because the reconstituted vaccine is slightly acid (pH 6·2–6·6), we know of no published evidence to suggest that immediate pain at the injection site is a problem.[3] We decided to investigate the matter further.

Subjects and methods
An inner city coeducational preschool population from a socially deprived area with a poor uptake of the MMR vaccine was chosen for the study. All children who had not been vaccinated were invited to attend for vaccination on one of two consecutive days. All children being vaccinated were accompanied by someone they knew well. Each child received 0·5 ml of vaccine subcutaneously through a 25 gauge needle into the deltoid region of the left arm. All vaccines were given by a single experienced doctor (RL). Crying after the injection was used as a measure of pain, and was assessed by the other doctor (FH). A randomised double blind study design was used, in which each vaccine was randomly selected from a previously coded lot and neither the doctors nor the recipients were aware of which vaccine had been used until the trial had been completed. Vaccinated children were kept separate from unvaccinated ones to avoid 'contamination'. Data were analysed by χ^2 test, Fisher's exact test, or Student's *t* test.

Results
Of the 97 children presenting, 20 cried before vaccination. Of the remaining 77 (37 boys and 40 girls), 37 (mean (SD) age 43·4 (11·1) months) received Pluserix and 40 (mean (SD) age 45·2 (10·7) months) received MMR II. There were no differences in the age between the groups or sex of the children.

The table shows the number that cried after vaccination. Children who received MMR II were 2·31 times more likely to cry than those who received Pluserix (95% confidence interval 1·16 to 4·60). Neither age nor sex were significantly associated with crying. Of the 28 children who cried after vaccination, none cried for longer than a minute.

Discussion
The results of this study suggest that pain is a real and unnecessary side effect of some MMR vaccines. Though we recognise that there are many difficulties in measuring pain, we feel that crying after vaccination is a reasonable measure

Incidence of crying after the two vaccines

	No who cried	*No who did not cry*	*Total*
Pluserix	8	29	37
MMR II	20	20	40
Total	28	49	77

in this instance, as we were able to control for many other factors that could be associated with crying (age, sex, social class, familiar location, presence of someone that they knew well, avoidance of 'contamination', skilled operator, and method). We are therefore satisfied that the difference in response to the two vaccines was the result of the difference between the two vaccines and not of some extraneous factor, and that the most probable cause for this was the acidity of the MMR II vaccine.

Although the difference is significant, one must keep in mind the clinical relevance of these findings. It could be argued that even those who did cry cried for no more than a minute and so the clinical relevance may not be obvious. However, this argument fails to take account of the fact that if one is given a free choice about whether to feel a 'little' pain or no pain at all, most would prefer to have no pain. In addition, those who give vaccines to children will be well aware of the effects of a crying baby on the accompanying parent or minder, as well as on other children who may be waiting to undergo a similar experience. Hence we feel that the findings are of clinical relevance.

This study was primarily carried out among children who had defaulted from the vaccination programme. The mean age of those studied is higher than that of the population of children targeted for vaccination. One cannot necessarily extrapolate the findings of such a study to a younger age group, given that so little is known about pain in babies and toddlers and the difficulties of measuring it.

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Tuberculosis in a contact

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Abstract

A 12 year old girl developed a large tuberculous pleural effusion. She was a contact of an adult with pulmonary tuberculosis who was positive on smear testing, and she had been managed in accordance with current British Thoracic Society recommendations.

The British Thoracic Society have recently published guidelines on the management of contacts of pulmonary tuberculosis.[1] We recently treated a child who developed tuberculosis from a known index case, despite being treated apparently in accord with these guidelines.

Case report

A 12 year old Asian girl was referred for investigation of a pleural effusion. She had been well until two days previously, when she became breathless during a physical education lesson, and was sent to the school doctor. A chest infection was diagnosed, but a chest radiograph showed a complete whiteout of the left hemithorax, and she was referred to hospital. On direct questioning she admitted to a two week history of a dry cough. She was an adopted child, and her adoptive mother (a doctor) was confident that she had had BCG vaccination at birth. Six months previously she had been seen in a chest clinic because the au pair girl, who had been with the family for two months, was found to have pulmonary tuberculosis that was positive on smear testing. Six weeks after the last contact with the index case the Heaf test was grade two positive, with a normal chest radiograph, and therefore no action was taken and no follow up appointment given. On examination her temperature was 37·6°C and she looked unwell. The only other physical signs were those of a large left pleural effusion. There was no scar of a previous BCG vaccination visible.

Investigations showed her haemoglobin concentration to be 124 g/l, white cell count $5{\cdot}7\times10^9$/l, platelet count 324×10^9/l, and erythrocyte sedimentation rate 38 mm in the first hour. She had normal urea and electrolyte, calcium, and phosphate concentrations and normal results on liver function tests. A Mantoux with 0·1 ml of 1 in 10 000 old tuberculin intradermally showed 15 mm of induration. A chest drain was inserted, and a total of 2·5 litres of straw coloured fluid was drained from the left chest. The pleural biopsy specimen showed necrotising granulomatous inflammation with Langerhans giant cells. Bronchoscopy was unremarkable. Pleural fluid and bronchial washings were culture negative for tuberculosis. She was started on pyrazinamide, rifampicin, and ethambutol because the organism in the index case was resistant to isoniazid, and she made a rapid recovery. Her mother subsequently rechecked the adoption papers, and found that the girl had not after all had a BCG vaccination.

Discussion

The development of a tuberculous pleural effusion in this child represents a failure of follow up. At the initial screening, there was a clear (but erroneous) history that BCG vaccination had been given. As the Heaf test was only grade two positive and the chest radiograph was normal, she was discharged, in accordance with the British Thoracic Society guidelines.[1] Had her true immune status been appreciated she would have had chemoprophylaxis. A single point in the history therefore made a considerable difference to her management.

In any case, BCG vaccination is known to afford incomplete protection (nil to 80% in different series[2]). It is possible that the development of a strongly positive Heaf test or chest radiographic changes would be delayed in patients only partially protected by BCG vaccine. Furthermore, the duration of protection after vaccination is unknown, and there is no good correlation between tuberculin hypersensitivity and immunity to tuberculosis.[3 4] It therefore seems to us to be safer to repeat the Heaf test and the chest radiograph three months as well as six weeks after the last known contact in all apparently negative children whether or not they have had BCG vaccination rather than to discharge them immediately from further follow up. The additional inconvenience is trivial, and, at least in this child, it seems likely that such a policy would have resulted in the earlier initiation of treatment.

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Indwelling cannula for insulin administration in diabetes mellitus

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Abstract

Experience with an indwelling subcutaneous Teflon cannula for insulin delivery to 10 children with diabetes mellitus is described. There were no significant complications during a one year trial period. The device may particularly benefit children during the early phase after diagnosis and for those with true needle phobia.

Multiple insulin injections may lead to distress and poor compliance in diabetic children particularly those of preschool age. We report the use of an indwelling, subcutaneous Teflon cannula (Insuflon, Viggo*) to give insulin to newly diagnosed diabetics and children who require a brief period of frequent insulin injections to regain adequate metabolic control.

Patients and methods

METHODS

The 24 guage Teflon cannula with an inner lumen diameter of 0·4 mm and an external diameter of 0·6 mm is similar in design to conventional cannulae used for intravenous treatment in neonatal units (figure A). The external end was sealed by a rubber membrane which covers a conical injection port. The total dead space of injection port and cannula is 0·0075 ml; this is equivalent to 0·75 units of insulin (100 units/ml). A topical anaesthetic cream containing lignocaine and prilocaine (EMLA, Astra) was applied to the skin one hour before inserting the cannula. After cleansing with alcohol, a roll of skin on the abdomen was lifted to insert the cannula subcutaneously at an oblique angle using a 0·4 mm steel stylet which was then removed. The device was secured with an adhesive patch (figure B). The cannula patency was maintained by the residual volume of insulin in the dead space.

PATIENTS

Ten children aged 4 to 13 years were studied. Five children had newly presented with diabetes, of whom three had severe ketoacidosis and required intravenous fluids and insulin. The subcutaneous cannula was inserted later to give short acting insulin every six hours. The other two newly diagnosed diabetics were given multiple insulin injections for 48 hours via the cannula and then changed to twice daily injections.

Two newly diagnosed diabetics were referred because they had refused twice daily injections of insulin. A cannula was inserted in both children without difficulty and they quickly adjusted to having regular injections.

The cannula was used in a further three

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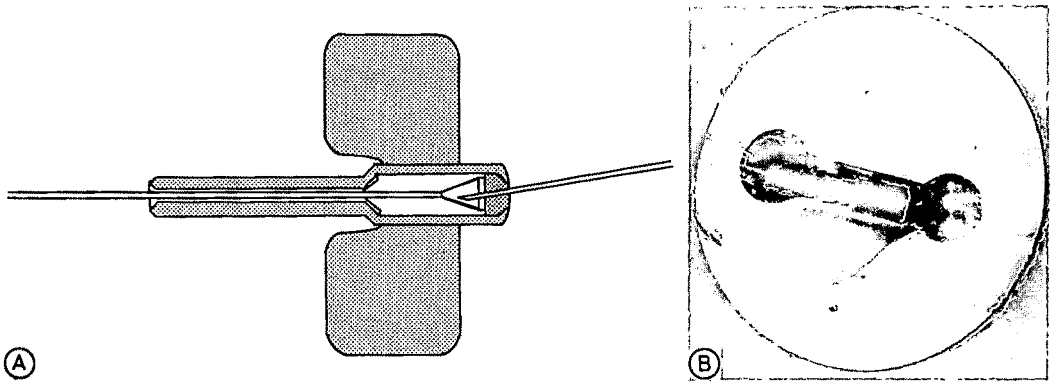
*The Insuflon device is manufactured in the UK by Viggo-Spectramed and distributed by Medistron Limited, 6 Lawson-Hunt Industrial Park, Brodbridge Heath, Horsham, West Sussex, RH12 3JR.



(A) Cross sectional diagram through cannula showing tip of needle in injection port. (B) Photograph of Insuflon in situ showing circular adhesive patch (tip of cannula to left of picture).

patients who needed a period of intensive insulin treatment during an intercurrent illness.

Results

The cannula was changed five days after discharge from hospital by a health visitor who was a specialist in diabetes. The parents continued giving insulin through the device twice daily and the period between change of site was adjusted for each patient. The mean duration in any one site was seven days, with a range of four to 10 days. All parents were able to replace the cannula themselves within two months of using this system.

Five patients continued to use the device at home for routine twice daily insulin injections over a period of three months to one year. Blood glucose profiles were comparable with other newly diagnosed diabetics and concentrations of glycated haemoglobin after three months, and in two cases, after six and nine months usage, were similar to those of other new diabetics attending our clinic.

At the end of the study period, two patients continued to use the device regularly, three patients having adapted to twice daily insulin injections without problem.

COMPLICATIONS

The only practical difficulty with use of the device was failure of the adhesive patch. Careful drying of the skin before application ensured that bathing, showering, swimming, and participation in energetic sports could be performed without loss of adhesion.

Minor complications included transient eczematous eruptions at the fixation site in two patients and the development of a small pustule at the insertion site in another patient. This followed prolonged use of the same site, the infection clearing once the cannula was resited.

Lipohypertrophy occurred in one patient who persistently used the same injection site. The problem quickly resolved when the cannula site was changed.

Discussion

Good metabolic control of diabetes leads to delayed onset, if not a lower incidence, of microvascular complications.[1] These may also be delayed by good habits being established soon after diagnosis.[2]

Most diabetics will continue to require regular, injected insulin for the forseeable future. Devices that make this less unpleasant are likely to improve compliance and discourage resistance to multiple injection treatment. True needle phobia is most common during adolescence[3] and may be the result of unpleasant experiences in earlier life.[4]

Studies in children[5] and adults[6] have shown that the subcutaneous cannula is well tolerated by diabetics of all ages. Using the device for multiple insulin injections leads to better compliance and improved metabolic control. Minor complications were similar to those reported in this study and generally resolved when the cannula was resited.

While the subcutaneous indwelling cannula was well tolerated and liked by patients and parents for ease of use and convenience, the relatively high unit cost means that this mode of treatment is probably not appropriate for routine general use in the child with uncomplicated diabetes. Those with true needle phobia or persistent abuse of one injection site, however, would benefit from the Insuflon device. A period of pain free injections may provide an easier phase of adaptation for newly diagnosed children and their parents.

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Autoimmune Addison's disease and thyrotoxic thyroiditis presenting as encephalopathy in twins

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Abstract

An 11 year old boy who presented with neuropsychiatric symptoms including delirium and pronounced agitation was found to have simultaneous onset of autoimmune adrenocortical insufficiency and hyperthyroidism. His identical twin also had hyperthyroidism and six months later developed symptoms of adrenocortical insufficiency. In children presenting with neuropsychiatric symptoms, adrenal (or pituitary) and other endocrine disorders should be considered.

Acute encephalopathy in childhood is difficult to diagnose and manage. Metabolic causes account for up to 12% of acute encephalopathies but specific diagnosis is often delayed until empirical emergency measures have been taken. Adrenocortical insufficiency may present with acute encephalopathy, and there are neuropsychiatric features in other endocrine disorders.[1] The range includes apathy, fatigue, social withdrawal, true organic psychosis, and—in extreme cases—coma.

We present a case of intermittent encephalopathy in a twin who was found to have autoimmune adrenocortical insufficiency and hyperthyroidism. Hyperthyroidism and adrenocortical insufficiency were also detected in his HLA identical twin brother.

Case reports

TWIN I

A boy age 11·8 years presented with wheezing of acute onset. He was treated for asthma and improved on regular nebulised salbutamol, intravenous aminophylline, and hydrocortisone. Twenty four hours after admission he became disorientated and seemed to be hallucinating. Plasma sodium concentration was 129 mmol/l and blood glucose concentration was 10 mmol/l while an infusion of 0·18% saline in 4% dextrose was in progress. Eight hours later he was lucid and could not recall the events of the preceding night.

When he attended for follow up one month later his mother reported that since discharge he had been tired and lacked energy. He often felt nauseated, vomited intermittently, and had headaches and vague abdominal pain. He had had nightmares, episodes of uncontrollable sobbing, and he reported feeling as if 'he was floating'.

Seven weeks later he was readmitted because of vomiting and dehydration. He was disorientated, agitated, and aggressive. His temperature was 37·7°C and pulse 136/minute and thready in character. Blood pressure was 90/60 mm Hg. No specific neurological abnormality was detected. Over the next four days his level of consciousness fluctuated with lucid intervals alternating with periods of disorientation, and he remained extremely agitated. There were no convulsions. Despite rehydration, his pulse rate remained raised and systolic blood pressure ranged from 120–150 mm Hg. He also had diarrhoea.

Management included rehydration with plasma followed by 0·45% dextrose saline and subsequently 0·18% dextrose saline, and correction of acidosis (pH 7·28, plasma bicarbonate concentration 13 mmol/l); 0·18% dextrose saline was continued for three days while the nausea and vomiting persisted.

Investigations showed: blood glucose on admission by stick test 1·8 mmol/l; plasma sodium concentration ranged between 130 and 138 mmol/l (on admission it was 133 mmol/l); and urea and creatinine returned to normal after rehydration. A random sample of urine contained sodium 52 mmol/l when the plasma sodium concentration was only 130 mmol/l. Plasma calcium was increased at 3·02 mmol/l (normal range 2·15–2·74), and phosphate was 1·38 mmol/l. Blood ammonia concentration was slightly raised at 80 μmol/l (normal <70). Aspartate and alanine aminotransferase activities were increased to five to six times normal, but settled over the next few weeks. Screening for hepatitis A and B viruses was negative. The haemoglobin concentration was 114 g/l, white cell count $3 \cdot 3 \times 10^9$/l (differential count neutrophils 10%, lymphocytes 59%, eosinophils 18%, and monocytes 13%); the platelet count fell to 89×10^9/l and occasional burr cells were detected in the blood film. Toxicology screen was negative. Urinary porphyrins were increased to 832 mmol/l (normal <320). Screening for plasma and urinary amino acids and urinary organic acids was normal. An electroencephalogram showed generalised raised amplitude slow wave activity compatible with encephalopathy. A computed tomogram of the head was normal.

He improved clinically after three days, and was discharged 10 days after admission. No cause for the encephalopathy was found.

He was readmitted three weeks later with vomiting, headache, abdominal pain, and polydypsia. He was not agitated or disorientated. Intravenous fluids were given to prevent dehydration and electrolyte imbalance.

Investigations to detect a possible metabolic defect were carried out, including search for porphyrins in the urine and (in view of the previously low plasma sodium) estimation of plasma cortisol concentration. When his mother was asked if she had noted any physical differ-

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Autoantibodies in family members

	Twin 1	*Twin 2*	*Sister*	*Sister*	*Mother*	*Father*
Age (years)	11·5	11·5	13	10	37	36
Gastric parietal	+	+	0	0	+	0
Adrenal	+	+	0	0	0	0
Nuclei speckled type	0	0	+	+	+	0
Thyroglobulin	+	+	0	0	0	Not measured
Thyroid peroxidase	+	+	0	0	0	Not measured
Thyroid stimulating hormone receptor (u/ml)	47·6 (strong positive)	8·2 (weak positive)	0	0	0	0

Mitochondrial, smooth muscle, and reticulin antibodies were not detected.

ence between the twins she volunteered the information that twin 1 had become pigmented. Although it had not initially been noticed, increased pigmentation of the palmar creases and the lower abdomen was present and was more striking when compared with his brother.

Primary adrenocortical insufficiency was diagnosed by a short tetracosactin (Synacthen) test (250 μg given intramuscularly) with plasma cortisol concentrations of 25 nmol/l at 0 minutes, 33 nmol/l at 30 minutes, and 32 nmol/l at 60 minutes. This was confirmed by a long Synacthen test (the baseline plasma cortisol concentration was 25 nmol/l and after three daily doses of Synacthen Depot 1 mg, 30 nmol/l). Plasma adrenocorticotrophic hormone (ACTH) concentration was 2000 ng/l (normal range 10–80). Ultrasound scan of the adrenal glands and plain abdominal radiograph were both normal. Bone age was 11–12 years (by the method of Greulich and Pyle).

At this stage he was noted to have tachycardia, warm extremities, lid lag, and slight diffuse enlargement of the thyroid gland, and he was fidgety. Thyroid function tests confirmed hyperthyroidism: thyroxine 230 nmol/l (60–140), triiodothyronine (T3) 4·7 nmol/l (1·3–3·2), T3 resin uptake 40% (25–34), free thyroxine index 92 (14–58), thyroid binding globulin 20 mg/l (17–28), and thyroid stimulating hormone (TSH) 0·1 mu/l (0·4–3·5).

Autoantibodies were detected against adrenal, gastric parietal, and thyroglobulin antigens, and thyroid peroxidase (table). TSH receptor antibody activity was 47·6 u/ml (strongly positive). Plasma B_{12} concentrations were normal. HLA typing of twin 1 and his brother showed A:24, A:-, B:39, B:40, BW:6, DR:3, DR:4.

He was treated with oral hydrocortisone, fludrocortisone, and carbimazole, which resulted in considerable improvement in both behaviour and well being. He is no longer fidgety, and his performance in school has improved substantially both academically and in physical activity. His weight had increased from the 3rd to the 75th centile and height from the 25th to the 50th centile. A repeat electroencephalogram was normal.

TWIN 2

The second twin was examined about six months after the first twin had presented. He had tachycardia, warm extremities, and his mother described him as fidgety like his brother, and argumentative. He had slight diffuse enlargement of the thyroid and his weight was on the 10th centile and height between the 25th and the 50th centile.

Thyroid function tests confirmed hyperthyroidism and a random plasma cortisol concentration was 180 nmol/l and plasma ACTH 270 ng/l. His autoantibody profile is shown in the table. TSH receptor antibody concentration was 8·2 u/ml (weak positive).

He was treated with carbimazole, and his mother was instructed to give him hydrocortisone during infections. As with his brother, the symptoms of hyperthyroidism responded promptly. Six months later (12 months after his brother's initial presentation) he developed symptoms of sweating and lightheadedness in the morning. A short Synacthen test (250 μg) showed a poor response as follows: plasma cortisol 299 nmol/l at 0 minutes, 286 nmol/l at 30 minutes, and 299 nmol/l at 60 minutes. He was started on regular hydrocortisone and fludrocortisone, and made a prompt and excellent response like his brother.

FAMILY

The autoantibody profiles of the mother, father, and two sisters aged 13 and 10 years are shown in the table. Thyroid function and random plasma cortisol concentrations were within normal limits for all subjects. Short Synacthen tests (250 μg) were carried out on the two sisters and were normal.

Discussion

The neuropsychiatric symptoms of twin I caused a considerable diagnostic problem and delay in diagnosis. We presume that the symptoms were caused by a combination of adrenocortical insufficiency and hyperthyroidism. In adrenocortical insufficiency correction of electrolyte imbalance alone does not result in improvement in the psychiatric symptoms.[1] We initially presumed that the hyponatraemia was caused by inappropriate secretion of antidiuretic hormone associated with a metabolic or encephalopathic disorder. It was probably exacerbated by our giving intravenous fluids of inappropriately low tonicity and was also presumably responsible for the electroencephalographic abnormalities indicating cerebral oedema. During his second admission other findings compatible with adrenocortical insufficiency were hypoglycaemia, hypercalcaemia, an increased proportion of eosinophils in the differential white cell count, and diarrhoea. The raised plasma aminotransferase activities, and ammonia concentrations and the presence of porphyrins in the urine may have been the result of transient liver dysfunction associated with hypoglycaemia, electrolyte imbalance, or hypovolaemia. The diarrhoea may also have been related to the hyperthyroidism.

These twins have autoimmune polyglandular syndrome type II, which has two or more of the following: adrenal insufficiency, hyperthyroidism or primary hypothyroidism, insulin-dependent diabetes mellitus, primary hypogonadism, myasthenia gravis, and coeliac disease.[2] There may also be vitiligo, alopecia, and pernicious anaemia. It is associated with HLA-B8, DR3, the peak incidence occurs at ages 20–60 years, and multiple generations may be affected. In contrast, the main features of type I polyglandular syndrome are hypoparathyroidism, mucocutaneous candidiasis, and adrenal insufficiency, with hypothyroidism occurring in a small proportion of cases. There is no HLA association, it usually presents in infancy or childhood, and siblings are commonly affected. In children with type II syndrome the combination of hyperthyroidism and adrenocortical insufficiency is rare.

Hyperthyroidism may develop before or after the onset of adrenocortical insufficiency,[3] but the simultaneous occurrence of the two conditions is rare at any age.[3–5] When thyroid and adrenal disorders coexist the onset of hyperthyroidism may precipitate latent adrenocortical insufficiency. Conversely, when there is hypothyroidism, thyroid function may improve after glucocorticoid replacement.

Adrenal insufficiency should be considered in any child presenting with neuropsychiatric symptoms. All children presenting with neuropsychiatric symptoms should have their blood glucose measured and if hypoglycaemia is found blood should be taken for plasma insulin, cortisol, and growth hormone concentrations before correction of the hypoglycaemia. Persistent tachycardia after electrolyte and fluid correction in autoimmune Addison's disease should suggest the presence of hyperthyroidism. Patients with adrenocortical deficiency should have thyroid function tested and a fasting glucose concentration estimated, whether or not symptoms of thyroid disease or diabetes mellitus are present.

Ideally relatives should have a history taken and a physical examination, and measurements of glucose (fasting), plasma thyroxine, and cortisol concentrations and an autoantibody screen every three to five years, especially between the ages 20 and 60 years.[2]

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AUDIT

Audit in child and adolescent psychiatry

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A statement of the aims of a child and adolescent service must be the starting point of any discussion of audit. They will be some combination of the following:

(1) Provide a service to children with emotional and behavioural, interpersonal, and developmental difficulties and their families.

(2) Offer a support, consultation, and a liaison service to other health, educational, and social service agencies in relation to children and their families.

(3) Function as a centre for teaching of students from medical, psychology, social work, nursing, and allied disciplines.

(4) Be a centre for innovation and research.

The first thing, therefore is to state the emphasis with which each of these four components is being offered. Teaching and research, for example, will be offered principally, but not exclusively by teaching hospital departments. Each aim carries its problems in audit.

Audit activity can be classified into three stages:

(1) *Input*: personnel and equipment on the one hand and patients and their problems or diagnoses on the other.

(2) *Process*: here the process of assessment, treatment, and management should be described.

(3) *Outcome*: this is the full appraisal of the results of assessment, treatment, and management.

The Royal College of Psychiatrists has recommended the use of clinical rather than medical audit.[1] As in nearly every branch of medicine and surgery, the service is offered by a multidisciplinary team, not just medical people. It is not helpful to try and split off a separate medical component except in the context of the study of a whole service. For this reason the comments in this article should be seen as applying, for the most part, to the child psychiatric team, rather than medically qualified staff alone.

Problems

(A) FINITE RESOURCES

In a recent publication on resource needs in child psychiatry the following areas of increased work were identified: marital breakdown (the divorce rate has almost doubled in 15 years); sexual abuse (an explosion in referrals recently); forensic work (the child and adolescent psychiatrist is spending more and more time in court, mainly on child care work); and teaching undergraduates and postgraduates, medical, and non-medical staff as skills and concepts developed by child psychiatrists and their colleagues are now seen as essential across a wide band of child care practice.[2] Also more time is needed for treatment, which is now more effective, and liaison work is on the increase in a variety of medical settings because modern paediatric interventions (neonatology, oncology, etc) are stressful to child, family, and staff. Children's homes have closed, resulting in many more requests for advice on management of children in the community. The list goes on, but the resources are finite, so managers are right to ask questions about how resources should be deployed.

(B) THE MARKET PHILOSOPHY

The government's solution is market forces. In this internal market measures of cost and volume will rule all unless we fight for an alternative with great vigour. Monetarist medicine has proved disastrous for health services in general in the United States[3] and will do so here, particularly in those specialties that elude neat short term packaging. These will include specialties interested in life span development and childcare such as child and adolescent psychiatry, community and developmental paediatrics, and preventive child health. Returning to our stages, the input stage can be costed and indeed monetary cost is an ultimate, though not the only important summary of input. It is how this financial input is deployed in terms of skill and equipment that is crucial. Process is the domain of quality assurance, the measurement of which is difficult but of great importance. The most important point, however, is that the processes that should be developed, and monitored, must be determined by our third stage which is the one of supreme importance. Without this output stage, audit is meaningless. It is not satisfactory to substitute valid outcome measures with a measure of cost. This means that monetary arguments must be powerfully countered by concepts and supporting data which measure the output of the service. I will return to this theme.

Input

(A) DIAGNOSTIC GROUPS

In common with the rest of medicine child disorders can be grouped by diagnosis. The main system in use in the UK was the International Classification of Diseases (ICD-9) which was introduced in 1978 and which is just being replaced by ICD-10.[4] A major contribution has also been made by the American Diagnostic and Statistical Manual (DSM-111R) system.[5] These schemes have contributed to a common language for child psychiatry and have helped to bring major conceptual advances into clinical practice. Two of these advances are so important that they merit mention here, although there are many more. The most fundamental is that diagnosis should be based on observable or reported data rather than concepts. Thus anxiety can be observed and reported by the child, while the 'oedipus complex' or the 'family system' are concepts, not empirical data. The second advance was the introduction in ICD-9 of the multiaxial approach to classification. This allows a series of statements about the child's situation—that is, as well as the psychiatric problem, their overall development, any developmental disorder, any medical condition, and the psychosocial situation can be coded. This means that links can be recognised, for example between child abuse (axis 5) and unsocialised disturbance of conduct (axis 1) or asthma (axis 4) and emotional disorder (axis 1). Such a common language is essential for audit, but uncritical adoption would be a mistake as diagnosis is but one reflection of the work required in assessment, treatment, and management in determining cost and outcome. A recent small study found that diagnosis does not predict of the amount of professional time needed on a case. Research is needed to find out if there is any way of predicting workload.

(B) RESOURCES AVAILABLE TO A SERVICE: THE DISTRICT PROFILE

It is very important to remember that the audit process cuts both ways. There is precious little point in a district employing consultants if they are not given the tools to do the job. In child psychiatry this has a whole range of implications that it has sometimes been difficult for managers to grasp.

The multidisciplinary team

There has been a tendency to have several separate services operated by, for example, child psychiatrists and clinical psychologists all operating independently or even in competition, with overlapping skills and often with a considerable degree of professional isolation. This problem figured in the Cleveland tragedy. It is important that different medical and nonmedical workers with children and families can call on each other's skills easily. With the increase in bureaucratic control and the line management principle in education and social services departments, and to some extent changes in the professional identities of nonmedical disciplines, it has become harder to develop and manage multidisciplinary teams. Useful questions can be asked at district level about how well services are organised in providing a service for children. In a recent study (AR Nicol, unpublished observations) it was found that while 94% of child psychiatrists worked in a multidisciplinary team, only half of these contained a clinical psychologist and only 21% contained an educational psychologist. Multidisciplinary teams are not self evidently the right way to organise a service, although there are strong arguments for them. Their working in itself could be audited—for example, how much time do team members spend trying to resolve, or avoid, interdisciplinary problems rather than getting on with their work?

Network of services

The second of our aims, the provision of consultation and support requires that, within a district, child psychiatrists be involved in a range of agencies. These could include a child development centre, special schools, children's homes, and so on. It is essential that this contribution is recognised by the appropriate involvement in joint planning and, for example, representation on the area child protection committee. This is another way in which the effectiveness of a service could be monitored.

Process

(A) CASE SUPERVISION

Historically, this is the earliest activity that could be called audit. The interview is the main clinical technique used in child psychiatry, both in diagnosis and treatment. What goes on in interviews is therefore of great importance. Training supervision should be divided between discussion of case management on the one hand and detailed dissection of interviewing style on the other. In earlier times, supervision was by an account of the therapy session written out afterwards and then reported to the supervisor. Numerous studies have shown that this form of supervision is unsatisfactory, for example in a study of medical students it was found that 54% of the themes identified in a videotape of an interview were not reported at a memorised account.[6] Supervision is often thought of as something that occurs in training only, but this should not be the case, as it is a most sensitive form of quality control. More recently, with the advent of family therapy the idea of live supervision has become more widespread and acceptable. Here the direction of the therapeutic interview can be influenced as it progresses, but we must ensure that senior colleagues are prepared to be audited in this way as well as trainees. Though it is important that constrictive procedures are avoided, there is room for the development of interview measures of quality, for example simple ways of classifying the aim of the interview and how well it succeeds in this stated aim.

(B) PEER REVIEW

In child psychiatry peer review is now becoming common, based characteristically on regional groups that have existed for some time. This can be by routine review of case notes and discussion of clinical practice. The most tangible outcome has been critique of the quality of record keeping.[7]

(C) HOW PROFESSIONAL TIME IS SPENT

A common perception is that consultants spend most of their time in committees. A diary study of 50 consultant child and adolescent psychiatrists gave a more optimistic picture.[8] Fifty two per cent of the sample were spending between 20 and 30 hours per week in clinical work whereas 42% of the sample (the mode) were spending between five and 10 hours per week in management: more than enough some might say. There was also substantial time investment in teaching, consultation, and travel. Diary methods such as this, if kept simple, are extremely easy and give a clear overview of time budgetting.

(D) LINKS AND COOPERATION WITH OTHER CHILD CARE AGENCIES

Managment of child psychiatric disorder demands cooperation with a network of children's services, not least the child's school. The quality of communication and cooperation with such agencies could be an important indicator of quality of the service.

(E) EDUCATION: SPECIALIST TRAINING

Under the auspices of the Joint Committee for Higher Psychiatric Training[9] child and adolescent psychiatrists have worked hard to develop high grade training programmes, particularly for senior registrars, this being the level at which specialist training occurs. Four years of training are recommended during which the trainee must be attached to several trainers and have a wide and prescribed variety of experience with a range of different disorders, both inpatient and outpatient, using the full range of treatments available. Log books of experience are kept in many schemes and regular supervision is compulsory. Other essentials are court work and experience of child abuse, children in care, and children with learning difficulties. The trainee must undertake research or a formal clinical innovation. The schemes are rigorously inspected and there have been disqualifications of schemes that haven't achieved the high standards expected. A district that appoints a child psychiatrist knows, nowadays, what skills they should be getting for their money.

(F) THE CHILD PSYCHIATRIST AS A TEACHER

Training of other medical staff at undergraduate and postgraduate level is a field that could be usefully expanded. The Association of University Teachers of Psychiatry has produced a statement of the topics in child psychiatry that may be usefully included in an undergraduate curiculum. An auditing process could help determine which of these approaches should be developed and which are less valuable.[10]

THE KORNER MINIMUM DATA SET

The Korner recommendations for management information for the NHS carries many problems for child and adolescent psychiatrists both as members of multidisciplinary teams and as consultants.[11] The team problem arises because the work of non-medical colleagues is measured entirely differently than that of medical staff. Clinical psychology, for example, is covered in a quite separate report. This makes the appraisal of collaborative work impossible. As consultants, the child psychiatrist shares problems with any specialist who practices substantially in the community for the following reasons.

(1) Korner focuses on general practitioners as a referral source, yet child and adolescent psychiatry serves the community best if referrals are taken from a variety of sources.

(2) Korner takes the referral letter as the measure of a case. Child and adolescent psychiatrists often see several members of a family and indeed others in the child's social network.

(3) Most important of all, the child and adolescent psychiatrist's work often consists of consultation with other professionals rather than direct with the patients. This mode of practice is specifically recommended by the Court report.[12]

PERFORMANCE INDICATORS

These are measures of quantity of work and have been developed by the Department of Health with the aim of identifying services who are statistical outliers which can then be studied more carefully. Our position as child psychiatrists is that better quality information on which to run the NHS is an urgent necessity; however it is dangerous to collect misleading information. The fact that all performance indicators are based on the Korner data makes them almost valueless for the reasons given above.

Assessment of outcome

This most important of activities can be discussed under two headings:

(A) RESEARCH ON THE EFFECTIVENESS OF TREATMENT IN GENERAL

The first point to make here is that this cannot be done by monitoring of everyday clinical activity. It needs high quality and adequately funded research. One of the tests of the government's vision and sincerity in the audit enterprise will be the degree to which this is understood. The question 'is child psychiatry effective?' is as nonsensical as asking if paediatrics is effective. Yet it has been seriously posed.[13] The problem has to be broken down into small testable hypotheses. Evaluation research into the assessment and treatment of children's psychological disorders has got off to a start, but far to slowly. Most intervention in child psychiatry comes under the heading of psychotherapy of one sort or another and although this is a field which has seen considerable advances in recent years, child psychotherapy continues to lag behind. What research there is tends to be encouraging—for example, there have been two meta-analytic reviews of the field that have each shown that child psychotherapy is associated with modest changes for the better.[14] [15] The problem is that they are based on basic research of variable and sometimes doubtful quality. The better studies, covering a variety of diagnostic groups treated in different settings,[16] [17] also show positive results, and indeed there is a trend for the better studies to demonstrate greater effectiveness. Family therapy too has shown promise in the management of antisocial problems,[18] child abuse,[19] anorexia nervosa,[20] and asthma.[21]

Recording of interviews and the rating of quality was the subject of extensive research in the 1950s and 1960s by Rogers and his school.[22] They found that there were qualities of the therapist that seemed to predict good outcome. The most consistent were emotional warmth and accurate empathy. More recently and specifically in the school setting, openness and assertiveness have been shown to be important.[17]

Treatment with psychoactive drugs forms a much smaller but nevertheless important part of practice.[23] The main drugs used are methylphenidate, which has been shown to improve attention span and disruptive behaviour in hyperactive children, antidepressant drugs, where trials in children have so far failed to show clinical therapeutic effects, and in tics and Tourette's syndrome neuroleptics are effective. Drugs should be given in the context of a total plan of management, including psychological approaches.

(B) THE EFFECTIVENESS OF A PARTICULAR SERVICE

The principle here should be to assess whether reputable treatment is being carried out under the best possible conditions: this is where process and outcome measures come together. The question of whether correct principles are being applied in the delivery of psychological interventions is an extremely difficult one. Direct supervision (see above) is one possibility. For some treatments the treatment programme is set out in a manual with suggested stages in the intervention.[24] This package can then be evaluated in rigorous clinical trials and then applied in practice. There has been some progress in this respect but application in ordinary clinics with limited resources is extremely difficult, if not impossible. It remains a sad truth that evaluative research does not necessarily guide practice. Clinicians are influenced by their previous training and by the techniques they feel comfortable with. As the amount and quality of evaluative research increases, it will be important to check takeup in clinic practice. At a more practical level, there are some ways forward: nonattendance and drop out rates. High rates don't necessarily reflect the quality of the service, characteristics of the family also exert an influence. They are, of course themselves a cause of inefficiency. Preparation for the initial appointment by telephone or a visit seems a worthwhile investment (RE Waler, unpublished observations).[25–27]

(C) CONSUMER OPINION

It is easy and most important to assess what the consumers think of the service. There are currently some projects on this topic in progress.

Computers can be seen as the 'US cavalry coming over the hill' or as the final nail in the coffin for a service struggling with inadequate resources and impossible demands. The truth is probably somewhere in between and some progress has been made. Two computer software systems have been developed for child psychiatry services[28 29] together with some interesting attempts at application.[30 31]

In conclusion it can be seen from this brief review that the official introduction of audit has implications for child and adolescent psychiatry, which apply also to many other branches of paediatrics. It may be worth bearing this in mind in the months and years to come.

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PERSONAL VIEW

Paediatricians and the new National Health Service

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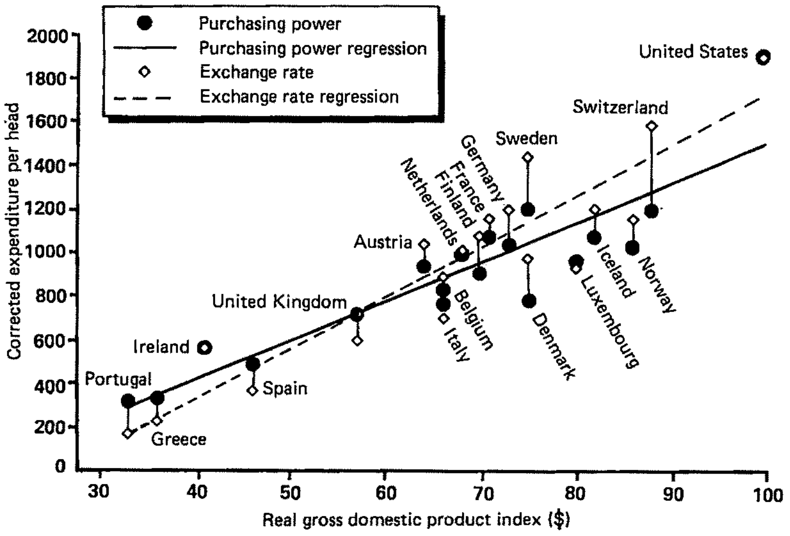
There is anxiety among paediatricians about the new NHS that is to be introduced in April 1991. Some concerns are shared by others from different disciplines who work in the NHS, some are particular to paediatricians. The purpose of this paper is to discuss the reasons for the changes and to suggest appropriate responses for paediatricians.

Background

The crisis about the funding of the NHS developed slowly over the decade after the introduction of strict control over public expenditure in 1976 as part of the terms of a loan from the International Monetary Fund to the British government.[2] Initially, inflation cause by pay awards over the cash limit was corrected in the subsequent year, but since 1982 financial management has included cumulative underfunding of pay awards so that service growth has relied on efficiency savings. It is tempting but unrealistic to wish to return to the days when a doctor could obtain the resources he needed to treat his patients simply by stating his case to his colleagues and the health authorities. It is also tempting to say that all that is required is to increase the proportion of the gross domestic product that is spent on health care in the United Kindom. This presumes that the amount spent in the United Kingdom is appreciably less than the country can afford and that the extra money can be raised either by taxation or by diverting money from some other area of public expenditure.



Total health care expenditure per head compared with gross domestic product for selected countries, 1986.[3] Expenditure is expressed in $ converted by exchange rates and purchasing power parities.

In the United Kingdom only half the amount/head of population is spent on health care compared with some other countries (figure).[3] Obviously the amount spent is related to the gross domestic product of the country, and the problem is mainly that of the relatively poor performance of the British economy, but that is not the whole story. The figure shows the amount spent on health care related to the gross domestic product of the country concerned. This relationship is shown with the currency conversions to $ made by money market rates. Conversions can also be made by relating different currencies according to what a unit of currency actually buys in goods and services in that country using purchasing power parities. Although such international comparisons are fraught with problems it seems that poorer countries buy more health care with less money, presumably because health care workers are paid less well.[4] Thus it is likely that some part of an increase in the proportion of gross domestic product spent on health care in a weaker economy will go towards increasing salaries rather than towards buying more health care; expenditure on health care in Canada is about 40% higher than in the United Kingdom, but the resources available for health care measured by purchasing power parities is about the same.[5] It is also useful to note that public satisfaction with the health care system in Canada (which has some features of the new NHS) exceeds that in the United Kingdom.[6] In addition, a larger proportion of the total funding of health care in the United Kingdom is provided from public expenditure than in most other comparable countries and even in Sweden more is spent on private care than in this country.

While we may argue that the government should give more money to the NHS, it is unrealistic to believe that our problems would then be solved. Over the last decade the demand for resources has totally overwhelmed the country's ability to pay. In spite of more doctors (how many paediatricians were there in your hospital in 1970 compared with now?), nurses and equipment, the introduction of intensive care for neonates and children, new treatments for cancer and previously fatal diseases such as renal failure, and many other factors affecting all age groups—not least the increased expectation of life—no country can meet all the demands of the whole population.[2] In the United Kingdom, for example, the increased provision for community services has led to the funding of the acute hospital sector being relatively restricted.

Clinical efficiency and effectiveness

The NHS is already rationed in the sense that not everyone can receive the treatment they want or occasionally need when they require it. The increasing dissatisfaction expressed by professionals in the service, by commentators and by patients,[6] led to the government's review and subsequent changes in the NHS Act.[2] Though there has been much criticism of the changes few credible alternatives have been presented. The underlying principle of the changes is to ensure that the money spent is used as efficiently and effectively as possible and, importantly, that equity is preserved.

We need to understand much more clearly what medical interventions are effective and what they cost so that their values can be assessed. The concept of value relates to the components of quality, quantity, and cost. Quality embraces both consumer satisfaction and medical outcome. In a service with limited cash quantity is also an issue of quality, because a high cost service with limited access may deny treatment to some who would benefit if a cheaper service was provided. One approach is to define acceptable standards of quality and then strive for maximum efficiency to increase quantity.

Many judgments about quality are necessarily subjective. None the less we have only to consider how many children have died or been severely damaged over many years by unnecessary tonsillectomies to realise that we do not have to look to the last century for examples of unnecessary and harmful medical interventions.

There is a need for much more rigorous examination of outcome of treatment in all disciplines, with more clinical trials and follow up studies.[7] The recent studies comparing streptokinase and higher cost alternatives for treating myocardial infarction are exemplary.[8] We need to recognise that low volume services are often of poor quality.[9] It is these concepts that underly medical audit and resource management, which are themselves key points in the new arrangements. They also underly the recent appointment of a director for research and development in the NHS to introduce new projects in this area.

Resource management (or clinical efficiency) and medical audit (clinical effectiveness) must be linked. To have a drive for efficiency without regard to effectiveness would be dangerous whereas the reverse is unrealistic in a service limited by cash.

The other key change in the NHS is that which separates the commissioners or buyers of health care from the providers and this is also directed at clinical efficiency and effectiveness. The concept is that informed professionals—either primary care doctors or the new health authorities—will decide on behalf of and with the patient what treatment should be purchased and from whom. It seems to me to be inevitable that this will lead to some treatments of doubtful value not being available on the NHS.

Those of us who work in secondary care, particularly in hospitals, will have to show that what we do is effective and efficient and ensure that our service delivers care of the quality and quantity that has been promised.

Organisation of hospital services

The changes outlined above will require serious alterations in the way we work and certain safeguards if the principles of medical practice are to be protected and if the vocational element in our contribution is to be satisfied. This latter point is often discounted but young people enter the NHS to serve, and most of the older doctors, nurses, and administrators have not lost sight of this vision; it sustains the service.

A fundamental change that is required is the management of hospitals by care groups or clinical teams rather than along the traditional functional lines. The tradition has been for each professional group to manage itself and for various groups (usually committees) to be used in an attempt to coordinate the activities of doctors, nurses, clerical staff, administrators, and so on. A little thought will enable the nonsense of such arrangements to be perceived. What matters is the service that is being delivered to particular groups of patients and all who contribute to this service need to manage themselves as a group. This implies that doctors, nurses, and others will work together, sharing responsibilities and even sharing tasks.

George Bernard Shaw remarked that all professions are a conspiracy against the laity, and sometimes the effect of specialisation between or within professions is to deny the competence of anyone else to carry out a particular function. As a paediatric nephrologist I need to recognise that not all children with kidney problems require my attention; indeed, to suggest otherwise would be inefficient to both the patient and the service—and even dangerous given the need to consider the whole child and family.

The care group should control its own costs and audit its activities in terms of clinical efficiency and effectiveness. It will require timely, accurate budgeting systems and will need to liaise with other groups and with the central hospital management and services. It is important to ensure decentralisation of responsibility and authority to the managers of the care group in equal measure. This is sometimes resisted, but to have responsibility without authority is demoralising whereas authority without responsibility is dangerous. Those who deny such arrangements should consider how else contracts can be negotiated and delivered.

The role of the doctor

The consultant together with other senior staff from other professions will have a key managerial role in such a care group. We believe that professional accountability to patients within each profession can be maintained by separating it from managerial accountability, which is concerned with the proper use of resources.[10]

If a doctor is to take a managerial role in a clinical group and maintain clinical competence (which is an important facet of leadership), however, then he or she will require assistance within a multidisciplinary team. In our hospital the paediatric director is assisted by a business manager and a nurse manager, and each of the five specialised clinical teams that comprise the directorate has its own budget with decentralised facilities and management arrangements.

The paediatric service

Paediatricians should urgently consider what comprises the child health service in their district, and argue persistently for proper management arrangements for it based on the principles outlined above.

The Court report recommended implementation of a dual system of provision of child care between primary and secondary care, with the community and hospital childrens services joining to provide a comprehensive service.[11] Under this scheme some professionals at present in the community services (such as health visitors) may be called upon to work with the primary services and family practices; others will join the secondary service.

The role of clinical medical officers must be defined and understood. They have many responsibilities which include: review of all handicapped children in mainstream education, the provision of selective advice to the school health service, the provision of service for children with special educational needs, initial assessment of suspected child abuse, the maintenance of the 'special needs' register, the evaluation of cases for court proceedings, and the clinical review of children in statutory and voluntary day nurseries.

These duties are in addition to routine child health surveillance and immunisations. As general practitioners and health visitors take more responsibility for routine tasks including screening we should be able to move towards reducing the number of clinical medical officers, while providing a more specialised and efficient service. This will happen only if the service is led by consultants and incorporates adequate training and career prospects that are comparable with those in other specialties within paediatrics.

The NHS has always insisted that it is a consultant led service and properly appointed consultants and principals in general practice are responsible for the training and actions of junior doctors. This principle should be maintained, with clinical medical officers being responsible to the district consultant community paediatricians.

Paediatrics is primarily concerned with development and the need to ensure that the impact of disease or disability on a child is minimised as far as possible, thus allowing the maximum potential to be achieved. Such a concept can only be embraced by integration of community and acute hospital services for children. Integration of health services for children is government policy (Secretary of State for Health. Letter to President of British Paediatric Association, 3 August 1989), but although government can play a permissive role it is a local decision to work out how best this can be achieved.

There is bound to be uncertainty as the new arrangements for separation between commissioning authorities and providers come into effect. For children's services it is logical for the acute hospital services and the community paediatric services to combine in a single care group. District general hospitals could be managed in conjunction with their 'outreach' services in child health, and probably in midwifery, mental illness and geriatrics.

'Outreach' services are those that provide continuing care in the community for those who have been treated in hospital. In addition to this, however—and more importantly—there are the community based services. It is appropriate for the base of these services to remain outside the hospital. This does not mean that they cannot be managed in the same unit as hospital services, with 'outreach' services and community based services combining into one single care group. Such a plan has been developed by Professor David Hull.[12] In addition, the British Paediatric Association has produced a policy document on the role of the consultant paediatrician (community child health).[13] This describes an integrated child health service and the role and training of clinical medical officers, senior clinical medical officers, and consultant paediatricians (community child health).

Integration of community and hospital services would in my opinion be facilitated by a common management structure and a common budget, but where this is not agreed then an integrated child health service needs to be ensured by other means.

The interface between primary and secondary services must also be organised. Many districts have divided their localities into 'patches' with a patch manager who is responsible for coordinating services. Under the new arrangements the patch manager could be responsible for both the provision of some services and the subcontracting of others from separate providers. The child health community service could then be subcontracted from the integrated hospital and community paediatric service. In addition the patch manager would serve as the liaison officer between the various providers including the relevant primary care services. Non-medical staff such as speech therapists, occupational therapists, physiotherapists, and health visitors are vital components of the child health service. Some will find it more appropriate to relate to primary care services based on general practice whereas others will be part of the integrated child health service.

If full integration of all staff who work in child health both in hospital and in the community into a common management structure is not agreed, then consideration should be given to all medical staff being managed within one unit so that appropriate training and flexible delivery of service is facilitated. Again the patch manager in the community could subcontract from the integrated child health medical service. A third possibility would be for consultant community paediatricians to have dual contracts with the acute hospital and community units, but this would seem to be less satisfactory. In any case it must be agreed that the clinical medical officers and the senior clinical medical officers are accountable both professionally and managerially to the consultant paediatricians (community health).

Conclusion

Changes in the structure of the NHS were inevitable given the problems that were created by the growing discrepancy between supply and demand. Whether or not the changes are welcomed we must understand them and the reasons why they have been introduced. Above all, paediatricians need to grasp the opportunity to improve the management of child health services and have a leading role in trying to ensure their success.

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REGULAR REVIEW

Bacterial virulence: an environmental response

J Simon Kroll

On meeting their hosts, most bacteria manage to establish a harmless colonising relationship, but occasionally tissues are injured leading to the local or widespread damage that we recognise as disease. In the search for new ways to fight such disease, we need to understand the steps in which microbes adapt to changes in their surroundings, the better to be able to target novel vaccines and other antibacterial treatments on the so called virulence factors involved. The issue is complicated by the fact that organisms undergo extensive phenotypic variation during infection. Some bacterial products are *only* made in such circumstances and not at all in laboratory culture, where conditions are very different to those found in the host. This review summaries some recent advances in our understanding at the molecular level of how bacteria respond to the changes they encounter in the course of infection.

Many infections start at epithelial surfaces, and a whole range of host defences are correspondingly directed at preventing mucosal colonisation. Mucus blocks access to cell surfaces while the coordinated action of cilia wafts mucus and bacteria away. In their turn, bacteria derive selective advantage from attributes that allow them to avoid this physical removal, of which the best characterised are the protein adhesins that anchor organisms to host cell surfaces. In order to minimise adverse steric or electrostatic interactions between closely apposed cells, these adhesins are often located at the tips of hair-like projections, the pili. Their adhesive properties notwithstanding, pili carry the potential *disadvantage* for the organism of providing a prominent structure for antibody attachment and for interaction with phagocytes. This can be resolved by the processes of phase (on-off) and antigenic (A↔B) variation.

Spontaneous phase and antigenic variation

Escherichia coli produces a pilus that allows it to stick to the mannose molecules found on the surface of many epithelial cells. Its expression is regulated by a flip-flopping on-off genetic switch. No gene can be transcribed until the transcriptional apparatus—RNA polymerase and any regulatory factors—correctly engages the promoter region upstream of the coding region on the chromosome. The promoter for this pilus gene is located on a spontaneously invertible segment of DNA, and pili can only be produced when it is oriented the right way round (fig 1A).[1] Under colonising conditions, the flipping of this DNA segment occurs rapidly enough to ensure that the stock of piliated organisms can be constantly replenished from non-piliated cells, and the merits of both phenotypes exploited. *Neisseria gonorrhoeae* shows an extra sophistication. Pilus mediated attachment to host cells is important to protect organisms in the urinary tract from being washed away. In chronic and recurrent infections, gonococci also need to avoid antibody mediated host defences on the uroepithelium. Organisms not only show phase variation between piliated and non-piliated forms, but can also produce a whole range of different antigenic types of pili through shuffling a set of genes coding for the pilus subunit (pilin). All the genetic machinery needed for production of one type of pilus is found in one chromosomal region, the expression locus, but parts of more than a dozen variant pilin genes are found in non-expressing loci elsewhere. Two mechanisms have been identified by which pilus type can vary.[2] In a spontaneous process termed gene conversion, any of these partial pilin genes can become spliced into the expression locus to lead to variation in pilus type (fig 1B).[3 4] Alterna-

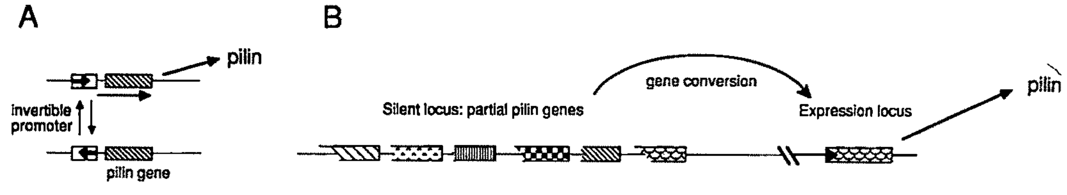

Figure 1 Pilus phase and antigenic variation. (A) The spontaneously invertible promoter of the E coli pilin gene only directs transcription and pilin production when in the right orientation. (B) In N gonorrhoeae partial pilin genes lacking essential DNA are copied by gene conversion into the expression locus where they are transcribed, leading to production of different pilins.

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tively, the lysis of gonococci in the course of infection can provide DNA to be taken up and incorporated into the chromosome of neighbouring organisms, splicing a 'silent' pilin gene into the expression locus in the process.[5]

Sensor-regulator mechanisms to control gene expression

The pilus gene rearrangements help organisms to persist in a changing environment through natural selection. However, the production of some bacterial factors may be needed only at one point in the sequence of steps in which an organism adapts to new conditions. A more favourable arrangement in these circumstances is for gene expression to be responsive to relevant environmental stimuli such as changes in temperature, pH, osmolarity, or nutrient supply. For this, bacteria need mechanisms for sensing the environment, processing information and responding accordingly, most efficiently by an alteration in the pattern of gene transcription. Numerous examples can be identified where the production of bacterial factors, including those implicated in virulent behaviour, is indeed environmentally responsive. The molecular basis for signal transduction—by which changes in the surroundings lead to changes in gene expression—has recently been elucidated, and in many cases involves two interacting bacterial proteins, one an environmental sensor and the other a regulator of gene transcription (fig 2).[6–8] The sensor protein spans the bacterial cytoplasmic membrane, its outward facing part responsive to a specific environmental signal, presumably through its affinity for some small ligand molecule. On binding the ligand, the protein is thought to undergo a substantial conformational change which allows it to interact with the second, cytoplasmic, component. The latter protein then becomes an active gene regulator, able to bind to the promoters of target genes and alter their level of transcription. There are many examples of virulence genes being controlled in this way. In *Salmonella typhimurium,* such a two component system regulates production of an outer membrane protein thought to confer resistance to toxic host factors in phagolysosomes.[9] In *Bordetella pertussis* a single two component system activated by temperature changes and other environmental signals governs the expression of more than half a dozen virulence genes—including those coding for pertussis toxin, fimbrial haemagglutinin, haemolysin, and adenyl cyclase toxin.[10]

Chromosomal supercoiling and global regulation of gene expression

Through the action of two component sensor/response-regulator systems, environmental changes lead to altered gene expression through the activation of regulators that go on to bind to specific promoters. The importance of another signal transduction process has recently been emphasised, in which environmental stresses lead, through changes in DNA topology, to alterations in the accessibility of promoters to the transcriptional apparatus. This provides a mechanism for organisms to respond to environmental changes with alterations in gene expression all round the chromosome.[11–13] The double helix of the bacterial chromosome is packed as a coiled coil—supercoiled—within the cell. The degree of supercoiling fluctuates constantly during bacterial growth through the shifting balance between the actions of enzymes continually twisting and untwisting the double

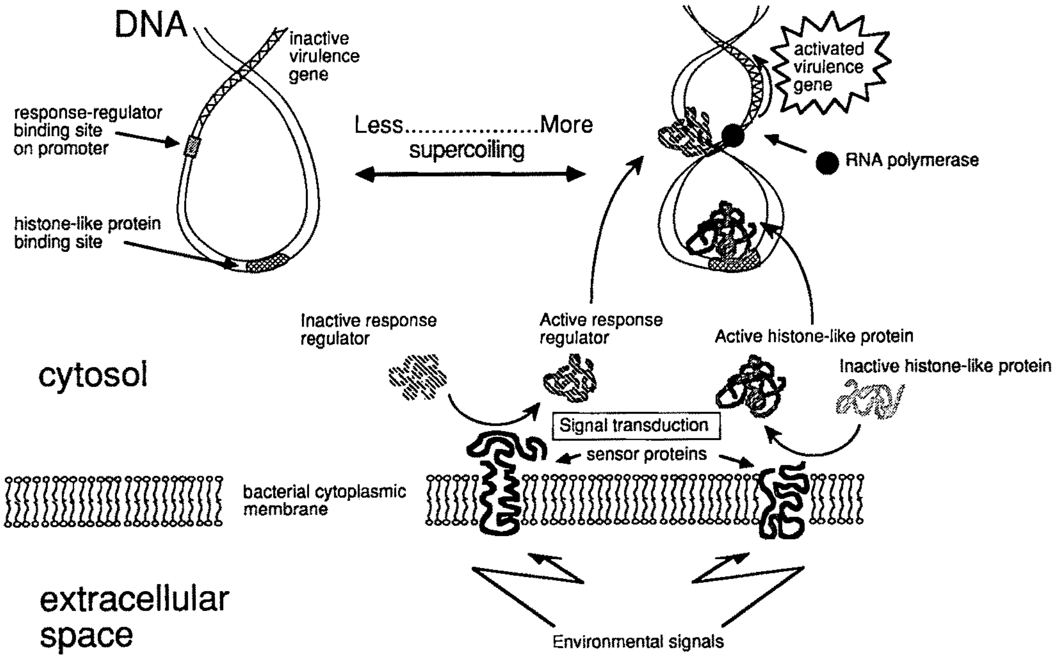
DNA
inactive virulence gene
response-regulator binding site on promoter
histone-like protein binding site
Less....................More
supercoiling
activated virulence gene
RNA polymerase
Inactive response regulator
Active response regulator
Active histone-like protein
Inactive histone-like protein
cytosol
Signal transduction
sensor proteins
bacterial cytoplasmic membrane
extracellular space
Environmental signals

Figure 2 Environmentally responsive gene regulation. The roles of response regulator proteins and histone-like proteins on the expression of a virulence gene. Sensor proteins are shown spanning the bacterial membrane, transmitting information to inactive cytosolic proteins. Once activated, the latter bind to appropriate sites on the DNA, leading to conformational changes that allow the RNA polymerase to engage the gene promoter and start transcription.

helix, and through variation in the production of DNA binding proteins analogous to the histones that are involved in the shaping of the eukaryotic chromosome. Studies on pathogens subjected to fluctuations in temperature, osmolarity and other stresses that occur on host colonisation have shown that DNA supercoiling levels are responsive to these changes.[12 14–16] Transduction of environmental signals into a supercoiling response can be envisaged through the action of the histone-like proteins, some binding to specific target sequences and others associating with the chromosome in a more non-specific way. One environmentally regulated histone-like protein, OsmZ, seems to bind DNA in a non-specific manner, altering its topology[12 17] and with this the expression of many genes. An important control function relating to virulent behaviour is suggested by the observations that mutations in the OsmZ gene accelerate the flip-flop regulation of *E coli* pili, increase production of *E coli* capsular polysaccharide, and derepress the invasion system of *Shigella flexneri*.[12 13 18] Another, known as IHF, binds to specific target sequences scattered through the *E coli* chromosome with profound effects on local DNA structure and gene expression, again including pilus gene regulation.[19]

Conclusion

As host-bacterial interactions are dissected at the molecular level, the hierarchical nature of the bacterial side of the equation is clear to see. Environmental responsiveness dominates the scene. Fluctuations in temperature, osmolarity, pH, etc are detected by the sensor molecules of two component systems. Conformational changes in these proteins allow information about the environment to be transmitted to gene regulators, which then attempt to activate their target genes. The effectiveness of the regulators will vary with the accessibility of gene promoters, modulated by the level of DNA supercoiling. The topology of the DNA will be influenced both generally and in a site specific manner by histone-like proteins, whose number and activity will also be environmentally controlled. The moment to moment coordination of gene expression—one aspect of which is virulent behaviour—represents the interplay of these overlapping factors. The molecular approach to the development of bacterial vaccines and other treatment strategies must take this into account. The study of organisms under laboratory conditions cannot be relied upon for the identification of critical determinants of virulent behaviour.

I am grateful to many colleagues, and in particular to Charles Dorman and Richard Moxon, for stimulating my thoughts on bacterial virulence.

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CURRENT TOPIC

HIV infection and haemophilia

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Families with haemophilia are in turmoil. In developed nations those of their members who were infected with HIV as a result of advances in the management of their bleeding disorder are dying. Not unexpectedly, many seek compensation for their infection, and it is difficult to ease the bitterness and anger of their plight until they have had an answer to their call either from the courts or from the government. For the most part people with haemophilia in the developing nations escaped HIV infection because their families could not afford blood product treatment. Their escape from the epidemic may or may not add years to their lives, because without treatment haemophilia itself will take its toll. In addition the advent of HIV infection has made the delivery of such treatment harder, because the safe manufacture of virally inactivated products has decreased the yield of the relevant clotting factors with consequent escalations in cost.

Against this turbulant background are set the needs of the parents of newborn haemophilic sons—the new generation with everything to play for and so much to lose. Before AIDS their future seemed assured. Haemophilia was no longer a major cause of premature death in the severely affected populations of developed countries, and the incidence of crippling with haemophilic arthropathy of major synovial joints had fallen. True, optimism about the effects of recurrent hepatitis was being moderated as evidence of long term clinical sequelae appeared many years after primary infection.[1] However, mortality from chronic liver disease had remained static for years and, certainly in terms of quality of life, the cost-benefit ratio was still very definitely in favour of multidonor blood product treatment with lyophilised factor VIII or IX concentrates. As well as the physical problems of haemophilia, associated social problems had also been eased considerably with contemporary therapy. Children with even the most severe forms of the disorder were able to attend normal school and compete in both the classroom and on the sports field with their non-haemophilic peers. Most had the same prospects for higher education, and could look forward to good long term careers unhampered by pain and disability or insurance or travel restrictions. The dreams of many died with the knowledge that they had been infected with HIV, sometimes—because of the sex linked inheritance of their disorder—along with a grandparent, brothers, uncles, or cousins. The scenario has been compared with descriptions of the first world war, except that in the case of haemophilia and HIV infection there is no respite with wives or girlfriends; HIV can, of course, infect them too, and the children born to them.

Present situation

Cumulative cases of AIDS reported to the World Health Organisation as of 1 March 1990 totalled 237 110.[2] Over half these cases (126 127) had been reported from the United States alone, suggesting considerable underreporting from many other countries. For instance, only 63 842 cases were known for the whole of Africa, and 94 from South East Asia, most of these from either India (44) or Thailand (37). Within the eastern bloc, despite all the recent publicity, only 74 cases had been reported from Romania and 26 from the USSR. Of the 9449 people known to be HIV antibody positive in the United Kingdom, 3346 cases of AIDS had been reported by May 1990.[3]

To what extent these latter figures are a true reflection of the state of the epidemic in this country is debatable. Probably the most accurate information comes from the haemophilic cohort because, in order to define the scale of infection, most patients were tested for HIV antibody early in the epidemic, before the recognition of problems addressed in current pretest counselling, and they have since been followed up for both their haemophilia and their infection. Of the 1201 people with haemophilia known to have HIV infection in the United Kingdom 194 (16%) had developed AIDS by the end of May 1990, and of these 130 had died. Details of the paediatric cases are shown in the table.

Progression to disease

With the exception of the newborn, who tend to fare badly,[4–7] infection with HIV in childhood

Children and adolescents with haemophilia and HIV infection in the United Kingdom

Age (years)	No with haemophilia A and B	No tested for HIV	No (%) HIV positive	No with AIDS	AIDS deaths
0–14*	863	464	80 (17)	11	5
15–19	424	305	128 (42)	9	4

*No HIV infected child is below 5 years of age. The data in the table is courtesy of the United Kingdom Haemophilia Centre Directors, 1990.

is usually followed by a prolonged latent period before the development of overt disease. Of the many variables that could influence the length of this period, only age has been shown to have a significant effect. An analysis of data from the continuing survey of 1201 HIV infected haemophiliacs by the UK Haemophilia Centre Directors showed that 85 had developed AIDS five years after seroconversion.[8] The younger the age at seroconversion the better the prognosis. In this study 4% of those under 25 years, 6% of those between 25 and 44 years, and 19% of those over 45 years had progressed to AIDS. These results have now been analysed together with those from Hershey, New York, and Pittsburgh to give the risk of developing AIDS by 7 years.[9] The authors conclude that, while it is likely that risk increases smoothly with age, 6% of those under 25 at seroconversion, 20% of those aged 25–44, and 34% of those aged 45 or more have developed overt disease. They estimate that the chances of AIDS occurring in the three age groups within the next year are 2%, 10%, and 11% respectively.

A similar finding, that only age at infection was found to have a statistically significant effect on the latent period, has recently been reported from a study of people infected as a result of blood transfusion.[10]

These and other studies of contributory factors that may influence the duration of infection have highlighted two of the difficulties in applying contemporary epidemiology to the counselling of infected individuals. Firstly, in most cases the date of infection is not known. Secondly, because a number of infected people die from causes other than those listed in the Centers for Disease Control case definition which is required for a diagnosis of AIDS, the true impact of HIV infection is always underestimated. In addition we may yet find that the overall prognosis for individuals with haemophilia may be influenced by concurrent infection with hepatitis B or C, and by difficulties in prescribing antiviral drugs in the presence of chronic liver disease or pancreatitis.

Growth and HIV infection

Perhaps surprisingly HIV infection seems to have little effect on the growth of haemophilic children, at least in asymptomatic patients. Pasi and his colleagues found no significant changes in the growth pattern of 27 boys followed up in Birmingham, despite the fact that some were symptomatic and one had developed AIDS.[11] The findings of a comparative study of 83 haemophilic children, 41 with HIV infection, in the United States were in broad agreement,[12] although the authors suggested that younger infected children may fare less well than older patients. They were also concerned about the histories of some individual children, and urged the setting up of a multicentre prospective study. In contrast to these preliminary findings in haemophilic children is the evidence of failure to thrive in those infected perinatally.[6] Whether or not this effect is primarily due to HIV itself or to other factors including secondary disease, malnutrition, or deprivation remains to be seen. In the context of haemophilia treatment these questions are important because of continued doubts about the long term effects of frequent transfusion of multidonor blood products, most of which contain substantial amounts of extraneous protein in addition to the relevant clotting factor.

Follow up and treatment

With increasing recognition of HIV infection as a chronic disease in which early intervention may be beneficial to long term prognosis, there is a need to provide for the comprehensive care of patients and families well before the onset of AIDS. The parallels with haemophilia care are obvious, and established patterns of referral and management of haemophilia have acted as a template for HIV and AIDS. In brief, comprehensive haemophilia care recognises six basic needs of patients and their families: accurate diagnosis, effective and safe treatment, 24 hour cover, regular follow up, expert counselling, and a good standard of communication about the disorder.[13] Because of the rarity of severe haemophilia much of this care falls to specialised hospital based units—the network of haemophilia centres—rather than to family doctors who usually have neither the experience nor the resources to treat the clotting factor deficiency. The same is true of HIV disease, although there will be exceptions, especially in areas of high prevalence. This is because, however good the support and counselling services within the community, the crucial medical need is for the prevention, or quick diagnosis and early treatment of opportunistic infections.

Most HIV infected haemophiliacs developing AIDS will present with *Pneumocystis carinii* pneumonia. Before this cardinal infection, oral candidiasis, herpes simplex, and herpes zoster are common, and we have noticed a flaring of acne in some adolescents who may otherwise complain of seborrhoeic dermatitis of face and scalp. Occasionally septic arthritis of a major joint occurs, and, short of aspiration, the differential diagnosis between infection and haemarthrosis can be difficult. Previous intercurrent exposure to hepatitis B and C viruses with subsequent underlying chronic liver damage may result in bouts of jaundice further complicating antiviral treatment. Infection with *Mycobacterium avium intracellulare*, or the appearance of a lymphoma are occasional terminal events. Kaposi's sarcoma is not a feature of HIV infection in the haemophilic population.

Many of these diseases can be prevented or at least ameliorated. All patients with persistently low or falling CD4 cell counts should be on prophylaxis for *P carinii* pneumonia. Opinions differ as to the best drug to use, although the general consensus is that inhaled pentamidine isethionate is indicated after the first episode.[14] The choice before this is between no prophylaxis, aerosol pentamidine, co-trimoxazole, dapsone, or pyrimethamine with or without sulfadoxine for asymptomatic patients[15]; current policy in the Newcastle Haemophilia Centre is to prescribe weekly dapsone.

Prevention of severe or sustained episodes of infection with candida is important both for the well being of the patient, and because oral or oesophageal thrush interferes with eating, adding to the problems of HIV associated weight loss and debility. Families should keep an antifungal preparation at home for use at the first sign of infection. Initially nystatin suspension is effective, but recurrent infection requires fluconazole. Similarly, early self medication with acyclovir will stem the development of herpes simplex infection, the painful and unsightly lesions of which can make life a misery for youngsters already very conscious of their body image and underlying disease. Although the local application of acyclovir cream is effective initially, recurrent infection demands early oral treatment. Seborrhoeic dermatitis usually responds to an antifungal (miconazole) or steroid cream and, when prevalent on the scalp, to a topical steroid (betamethasone 0·1%). Isotretinoin given under expert supervision may be needed to bring acne under control.

None of these measures has, of course, any effect on the underlying HIV disease, but there is increasing evidence that zidovudine (AZT, Retrovir) does. After a trial (protocol 019) of the drug in asymptomatic patients in the United States[16 17] the Food and Drug Administration (FDA) has recently extended the licence for zidovudine from its already established use in symptomatic people to symptom free HIV infected patients with CD4 counts below 500/μl.[17] Given continued concern about possible long term side effects and the cost of the drug, it is not surprising that the rationale behind the FDA decision has been questioned, both in the United States[18] and in Britain,[19] where a Medical Research Council placebo controlled trial in asymptomatic patients (Concorde I) continues in association with the French INSERM organisation.

Neither the United States nor the European trial has included patients under 18 years of age, and recommendations for treatment below that age are sparse. Given current knowledge all that can be said is that zidovudine should be prescribed to all symptomatic children, and it should be seriously considered in all asymptomatic children with persistently low (<500/μl) or falling CD4 counts. Present dosage recommendations for adults (from the 019 trial) are 100 mg zidovudine five times a day in waking hours.

Finally, there is now enough evidence to recommend that all HIV infected children should receive regular prophylaxis with intervenous gammaglobulin in order to correct hypogammaglobulinaemia and reduce the incidence of intercurrent infections.[20–22] Although all children should have received routine active immunisation, with the exception of BCG which is contraindicated in HIV infection, the immunosuppression of the underlying disease results in progressive loss of antibody and booster doses or additional protection may be needed after exposure to infection.[23]

Schooling

With the exception of occasional flurries of parental or teacher anxiety in a few schools early in the course of the epidemic, the education of most HIV infected children has proceeded without hindrance. This has been due chiefly to the common sense of teachers, backed by the government publication on schoolchildren in May 1986,[24] and to the efforts of local education authorities and their medical advisors. Fundamental to this response was the evidence, which has remained unchanged with time, that HIV is not a contagious disease, with no risk of transmission in the everyday, non-sexual activities of school or work.

Also fundamental, to the care of children in particular, was the strong plea for the child's right to privacy that was made in the original government booklet, together with the recommendation that knowledge of infection be 'rigorously confined to those who need to know'. Although immensely reassuring to parents and infected youngsters it is perhaps unfortunate that this advice is still necessary today, because it implies that there is something different about HIV infection and AIDS that negates the usual rules governing the professional confidentiality of doctors and teachers. Without an appreciable change in public perception, however, people with HIV infection and their families will continue to be terrified of exposure, and in particular of the threat of attention by the more insalubrious sections of the media.

As a result, despite both official and individual reassurrance, it is still unusual for permission to be given to tell schoolteachers or school medical officers about the diagnosis. This interrupts the free exchange of information that can help children with learning or social difficulties, and must put the child with the secret knowledge of his or her infection at a special disadvantage. HIV infection is a very lonely condition to bear, especially when surrounded by active, healthy children working towards careers and future sexual and social lives unclouded by thoughts of disease and premature death. At least in the case of haemophilia teachers with knowledge of the primary diagnosis are able to make an informed guess and act accordingly, but where there are no clues infected children have to either divulge their status or be obviously sick before help can be given. One further point: paediatricians looking after cohorts of haemophilic children should not give a child's HIV antibody status, whether positive or negative, to the education or other authorities because this will lead by exclusion to diagnosis of HIV positive patients, sometimes erroneously.

The adolescent

For many people HIV infection forces dependence on others at precisely that time of life normally associated with increasing independence. This dependence has to be handled with sensitivity and recognition of individuality, so that the confidential trust that is of paramount importance to the care and management of the HIV infection can be established between the young person and his or her adviser.

Those with haemophilia should be at an advantage here because of their close links with hospital staff over the years,[25] although in some centres the transition from paediatric to adult care may mean that the relationships have to be broken at an especially difficult time. Whatever the background, all infected adolescents need time to express their views and concerns in private, and they need the discipline of regular informal appointments for both counselling and careful and reassuring physical examination. Specific attention should be paid not only to their general health but also to advice concerning their activities and interests and their future thoughts about competitive examinations and career. Not unexpectedly, it is easy for the infected adolescent to give up all hope of a structured and worthwhile future. Not only do they feel cut off from their peers because of their infection and the secrecy surrounding it, but they sometimes see no point in trying to achieve anything.

Friendly inquiry should be made about their use of alcohol, tobacco, and drugs and about diet, sleep, and their family and other relationships. The normal vulnerability of adolescent boys and girls can be made intolerable by the difficulties imposed by HIV infection on the establishment of normal loving relationships. Sometimes the person to help guide youngsters through these difficulties is a mature practice nurse or young counsellor, rather than a doctor, social worker, or psychologist. Whoever undertakes the task must be prepared to give repeated help when it is needed. Of the many publications written to help people come to terms with the problems of sexuality and HIV infection, one of the best is that recently published by the British Haemophilia Society.[26]

During sessions with infected adolescents, topics that should be covered in addition to those already mentioned and with reference to the age and maturity of the youngster, include repeated reassurance about casual spread, sexual relationships, the prevention of infection in others, and death and bereavement.[27] The adolescent should be given the means for immediate access to help, including the free provision of condoms and advice about their use and that of preparations containing nonoxinol 9. He or she should know that nursing will be by people already known to them if hospital admission is necessary, and that financial help will be made available for friends and family making visits to the clinic or ward.

Most adolescents will wish to share fully in knowledge about their progress and the results of investigations, coupled with information about currently available treatment. Concerns about the availability and wisdom of such treatment, often fostered by ill conceived television programmes, are easily transmitted to patients and add to the uncertainties associated with their underlying disease.

Current treatment of haemophilia

Most HIV infection in the haemophilic population occurred before the virus was discovered and therefore before individual donor testing was introduced. As a result of the exclusion of high risk donors, HIV antibody testing, and the treatment of concentrates to remove viruses no further cases of infection have been reported since 1986. Although initial attempts at viral elimination using dry heat sometimes failed,[28–31] newer methods involving the use of monoclonal antibodies together with heating, or solvent/detergent breakdown of the fatty envelopes of HIV and other viruses seem very safe, as does prolonged dry heating at 80° for 72 hours in the final phial, which is the method presently in use in the UK. However, after all that has happened no-one is foolish enough to give an absolute guarantee on the safety of any product, and occasional reports of failure to eliminate hepatitis C still occur.[32]

People with severe or moderately severe haemophilia who need factor VIII or factor IX replacement therapy should no longer be treated with fresh frozen plasma or cryoprecipitate, because these products cannot yet be treated in any way to remove virus that has remained undetected on individual donor testing. The choice for them therefore lies between the Bio Products Laboratory concentrates (or the equivalent products of the Scottish Blood Transfusion Service), the products of the French company Bio-Transfusion which also come from volunteer donors but are treated with solvent/detergent, or, in the case of factor VIII, the two commercial products prepared from the plasma of paid donors that have full licences in the UK. They are Monoclate-P, manufactured by Armour, which is prepared by monoclonal antibody separation together with pasteurisation, and Profilate, which is manufactured using the solvent/detergent method by Alpha. Neither the British nor the Bio-Transfusion products are yet licenced in the UK, although the latter do have full French licences. Whichever product HIV and hepatitis C negative patients receive they must continue to be followed up regularly and agree to regular testing for evidence of infection. This is because it has not proved possible to identify HIV in individual phials of factor VIII or IX, and evidence of safety must therefore depend on careful epidemiological surveillance. Mildly affected haemophilia A patients should, when possible, be treated with desmopressin (DDAVP) rather than blood products as should carriers, and people with type I von Willebrand's disease. All patients with a haemostatic disorder that may need blood product correction at some time should still be vaccinated against hepatitis B, as should staff involved in their care.

Compensation

The governments of many countries have responded to appeals from haemophilic families for extra help in order to cope with HIV infection and AIDS.[33] Within the UK this response has been based on recognition that HIV infection has resulted in additional hardship for a group of people with pre-existing handicap. Two payments have been made, the first of £10M into a trust fund in 1987 (the Macfarlane Trust),[34] and the second, in 1990, of individual ex-gratia payments of £20 000 to the estimated 1200 people with haemophilia and HIV infection.

Given the nature of their infection it is not surprising that these measures, although very welcome, have failed to stop legal action, and some 950 people are currently seeking substantial compensation through the courts. The magnitude of the task facing both plaintiffs and the defence is formidable, and although everyone concerned is aware of the urgency involved as AIDS takes its toll in the haemophilic population, it is unlikely that, without government intervention, a decision will be reached before the autumn of 1991. In the meantime the action causes additional misery, both because of difficulties in the hospitals and departments concerned and, more importantly, because of the disruption of the normal human processes of adaptation and grieving that cannot progress until the dispute is resolved one way or the other.

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Addendum

In December 1990 the government offered to settle the UK legal action without admission of liability. As we go to press the terms of this offer are being considered by the families involved. Claims for compensation continue in other countries.

LETTERS TO THE EDITOR

Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death

SIR,—In a recent paper Dr Southall *et al* suggest that rapid shunting of unoxygenated blood through the pulmonary vascular bed is a cause of sudden and unexpected death in infants and children and that this may be causally related to the sudden infant death syndrome (SIDS).[1] This assertion is based on the occurrence of sudden death in eight of their 51 patients (16%), four of whom died during cyanotic episodes.

While the hypothesis and the physiological evidence for it are interesting and well presented, review of the fatal cases reveals that five of the eight had concurrent pathological processes that are independently associated with sudden death, and in some cases they had cyanosis: impacted intraoesophageal bolus of food in a patient with a repaired tracheooesophageal fistula (n=1), bronchopneumonia (n=2), bronchopneumonia with mucus within airways (n=1) and a brainstem glioma (n=1).[2 3] It would strengthen the underlying hypothesis considerably if further information could be provided detailing how these well established causes of sudden death were eschewed in favour of intrapulmonary shunting as the prime mechanism responsible for death. Of even more importance is the need for clear documentation of the evidence for intrapulmonary shunting in the eight fatal cases, if this is to be accepted as the cause of death. It appears from the text that only one patient had contrast echocardiography (case 18) and that none had krypton infusion scans or postmortem injection studies. It would clarify matters considerably, therefore, if the antemortem and postmortem evidence for shunting in each of the fatal cases could be provided.

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1 Southall DP, Samuels MP, Talbert DG. Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death. *Arch Dis Child* 1990;65:953–61.
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Drs Samuels and Southall comment:

Dr Byard has raised important questions concerning our hypothesis that severe hypoxaemic episodes may cause sudden death in infants and young children. The presence of a structural abnormality at postmortem examination does not in itself always explain the *cause* of death. The cessation of cardiorespiratory and cerebral function must ultimately encompass a physiological mechanism. In our patients, the findings of bronchopneumonia, an intraoesophageal impacted food bolus, and a brainstem glioma were alone insufficient, in our opinion, to explain their sudden and unexpected deaths. Two died during the night without any premonitory symptoms or signs, while the other three died during typical cyanotic episodes.

In all eight cases, our patients had suffered repeatedly from sudden and life threatening cyanotic episodes needing resuscitation. In the absence of physiological recordings *during* their deaths, we can only speculate as to the mechanism which caused their death based on the investigation of living infants undergoing similar hypoxaemic episodes having characteristics that could be described as life threatening. Although some of our patients did not undergo *all* the investigations required to confirm the development of an intrapulmonary shunt during their cyanotic episodes, their episodes were identical in all other respects to those occurring during krypton infusion scans or contrast echocardiography. Intrapulmonary shunting remains one of the best explanations for the sudden development of their life threatening hypoxaemia. How and where in the lungs this shunt occurs remains to be elucidated.

At present, an explanation for the final pathophysiological pathways leading to sudden and unexpected infant deaths, even in the presence of abnormal postmortem findings, remains unresolved.

Measles immunisation

SIR,—Active immunisation is efficient in preventing the central nervous system complications of measles.[1] The wisdom of current recommendations[2] on measles immunisation is illustrated by a case of progressive measles encephalitis after renal transplantation for treatment of the congenital nephrotic syndrome.

Immunosuppressive treatment after successful renal transplantation (age 6) was with azathioprine and prednisolone. The primary renal disease (congenital nephrotic syndrome) was considered to preclude pretransplant measles immunisation. At 10 years of age the child had a 'flu-like illness' with morbilliform rash. Three months later she suffered a second 'flu-like' illness and within days, developed myoclonic seizures involving arms, head, and subsequently legs. An electroencephalogram showed periodic and stereotyped bursts of high voltage slow components accompanying the clinical events. Seizures were absent during sleep; conciousness and intellect were preserved when awake. Anticonvulsant treatment was ineffective. Intrathecal synthesis of measles virus antibody was documented (serum titre 40, cerebrospinal fluid 4 in presence of normal blood cerebrospinal fluid barrier function; cerebrospinal fluid/serum albumin $2{\cdot}4\times10^{-3}$). Rubella virus antibody (serum 640, cerebrospinal fluid <1, serum rubella virus IgM only weakly positive) was also found at this time but neither antibody was detectable in serial serum samples collected prior to the first 'flu-like' illness. Antibody titres were unchanged in a subsequent serum sample suggesting both measles and rubella to be temporally associated with the first illness (the second remained undiagnosed). Four months after the onset of seizures she developed chickenpox, lapsed into coma, and died six weeks later without regaining conciousness. Chickenpox probably accelerated the clinical course but not by direct central nervous system invasion (serum Herpesvirus varicella 320, cerebrospinal fluid <1).

It is possible that rubella either triggered a latent measles virus infection (although we found no serological evidence of previous measles) or, interfered with the normal measles immune response (compounding the effects of immunosuppression) leading to progressive central nervous system infection.[3] Whatever the mechanism, this case reinforces the view that *all* children going forward to renal transplantation should receive measles immunisation.

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Reflux vomiting

SIR,—It was kind of Dr Milla to refer to some of my publications in his article on reflux vomiting.[1] Unfortunately some of his interpretative conclusions require correction. Like many other writers on this subject he has totally misrepresented my 1959 observations on the natural history of vomiting infants with a partial thoracic stomach (hiatal hernia)[2] as being applicable to all infants with 'symptomatic gastro-oesophageal reflux'. This is most certainly not so. His quote relating to the incidence of gastro-oesophageal reflux is equally misleading as the hospital estimate of one in 500 to which he refers relates to the hospital attendance of children with a partial thoracic stomach and not to that of children with reflux per se as mentioned in his article. Clearly the number of infants attending hospital with reflux and no recognisable displacement into the thorax of the gastro-oesophageal sphincter would be greatly in excess of this figure. I am also perplexed by his statement that 'The finding of a hiatus hernia with or without an associated partial thoracic stomach is not of itself an indication for surgery'. I have tried substituting gastro-oesophageal reflux for hiatus hernia and for partial thoracic stomach but in neither instance does this alteration clarify the meaning of this sentence in the particular context of his article.

Largely as a result of the emphasis placed on the importance of gastro-oesophageal reflux per se and its detection by nonradiological means very much less attention is directed nowadays to the identification of a partial thoracic stomach, which is often regarded as having little clinical relevance. I have, however, found on long term clinical evaluation of many hundreds of infants with reflux that the presence or absence of a partial thoracic stomach serves as a very valuable clinical guide to prognosis.[3] For whereas reflux in infants with a partial thoracic stomach is associated with a significant morbidity, gastro-oesophageal reflux in the absence of this anomaly is a relatively benign self limiting condition, which in the case of vomiting infants can usually be treated successfully by appropriate and adequate thickening of feeds.[4] I am therefore in no doubt as to the *clinical* importance of distinguishing infants with reflux and a partial thoracic stomach (in whom the antireflux contribution of the abdominal oesophagus is absent) from those with reflux as the only observed abnormality. Such reliance on the prognostic significance of a partial thoracic stomach is of course totally dependent on having an experienced paediatric radiologist as a colleague who is equally aware of the importance of carefully examining infants with reflux for a partial thoracic stomach.

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Les Blicqs,
St Andrew's,
Guernsey,
Channel Islands

1 Milla PJ. Reflux vomiting. *Arch Dis Child* 1990; **65**:996–9.
2 Carré IJ. The natural history of the partial thoracic stomach (hiatus hernia) in children. *Arch Dis Child* 1959;**34**:344–53.
3 Carré IJ. Clinical significance of gastro-oesophageal reflux. *Arch Dis Child* 1984;**59**: 911–2.
4 Carré IJ. Management of gastro-oesophageal reflux. *Arch Dis Child* 1985;**60**:71–5.

Growth after gut resection for Crohn's disease

SIR,—We read with interest the paper by McLain *et al*, and we would like to comment on both the methodology of their data collection and the authors' conclusions.[1] Firstly, this was a retrospective study, and thus has the major disadvantage of lacking standardisation in the collection of the auxological data. There is no mention in their paper of how height measurements were recorded and standardised, or on the accuracy of the staging of pubertal development.

Secondly, while agreeing with their findings that dramatic growth acceleration may occur after surgery for Crohn's disease, we disagree with their conclusion that 'catch up growth is not limited by the stage of puberty'. We have recently completed a large, prospective study investigating factors influencing growth after bowel resection for Crohn's disease in 42 children requiring surgery before their 17th birthday. All growth indices (including height measurements every three months) were performed prospectively by a clinical auxologist, and an accurate pubertal staging was performed in each patient at the time of surgery, together with the radiological bone age in the majority of cases. Our data (table) clearly show a strong relationship between height velocity in the first postoperative year and the pubertal status (Tanner breast and genital stage) at time of operation. The apparent lack of effect of pubertal status on growth in the study of McLain *et al* may merely reflect the very small number of children in advanced puberty (one), or the retrospective nature of their data collection. In our opinion, the timing of surgical intervention is vital, and should be performed before puberty becomes too advanced and the potential for catch up growth is lost. This is in direct contrast to the conclusion stated in their paper.

Mean preoperative and postoperative height velocities (cm/year) in 42 children undergoing bowel resection for Crohn's disease grouped according to pubertal status at time of operation

	Boys		*Girls*	
	Before surgery	*After surgery*	*Before surgery*	*After surgery*
Prepubertal: stage 1 (n=18)	1·85	7·40*	1·64	9·08*
Early puberty: stages 2 or 3 (n=14)	2·81	8·20*	2·23	7·14*
Late puberty: stages 4 or 5 (n=10)	3·32	4·50†	2·87	3·09†

*p<0·0001, †p=not significant.

Finally, we monitor growth very carefully in all our children with Crohn's disease. Any patient whose growth appears to be suboptimal is referred to a joint paediatric inflammatory bowel disease/growth clinic every three months, which is staffed by a paediatric gastroenterologist, a paediatric endocrinologist, and a clinical auxologist, to determine the appropriate strategy for managing the problem (for example, surgery) at an early stage.

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J M W KIRK
M O SAVAGE
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1 McLain BI, Davidson PM, Stokes KB, Beasley SW. Growth after gut resection for Crohn's disease. *Arch Dis Child* 1990;**65**:760–2.

Drs Davidson and Beasley comment:

Thank you for the opportunity to reply to the correspondence of Evans *et al*. We agree completely with their comments regarding the relationship of the timing of surgery to puberty on catch up growth in Crohn's disease. Although we acknowledge that we have insufficient patients in advanced puberty to comment on the effect on growth of the stage of puberty, our data would suggest that catch up growth is not limited by the onset (as distinct from stage) of puberty. The one patient in advanced puberty clinically who exhibited catch up growth after surgery did not have his bone age assessed.

Like Evans *et al* we would emphasise the importance of careful ongoing growth measurements in these children. The use of a multidisciplinary team provides optimal management of children with Crohn's disease.

Finally, we are pleased to find that the prospective data of Evans *et al* support our retrospective observation.

SPRING BOOKS

The paediatric departmental library

What should be the priority for the paediatrician when financial considerations reign and access to current literature is still via books and journals? The rate of change in paediatric practice and slowness of publication in journals and especially in textbooks lead to such a rapid obsolescence that departmental libraries are rarely of use for any in depth study. They provide a source to back up basic case presentations but at a considerable expense. It is impossible to shortlist key titles as every paediatrician has a favourite selection of titles that have proved to be of particular value. These titles have often been selected because the paediatrician has been asked to review that particular book or because a particular subject caught his/her eye from browsing through the unsolicited mailed catalogues or at bookshops at conferences. Most medical schools are persuading departments to adopt a centralised library system for the sake of more efficient lending schemes and security. So what does the paediatrician provide for the juniors who rarely have time to reach the central and sometimes distant library?

There must be the equivalent of a paediatric encycylopaedia covering most common subjects, such as the *Textbook of Paediatrics* by Forfar and Arneil or Nelson's *Textbook of Pediatrics*. Then a selection of system or disease based textbooks should be available. The exact proportion of the subjects will depend on the case mix of the unit. Most general paediatricians will have these books but whether they can be maintained in their current editions is unlikely at present. A cheap but effective way of maintaining a more up to date reference for junior staff is to organise a file of review articles from paediatric journals or free journals such as *Hospital Medicine, Medicine International, Update, Hospital Update, Prescriber's Journal,* and *Drugs and Therapeutics Bulletin*. The difficulty is the archiving and security. However the availability of photocopiers has made this easier, although care must be taken to avoid infringing the copyright laws. Another very useful practice is to incorporate a photocopy of a key article in the hospital notes of the patient with this particular diagnosis. It is important to keep updating this and to include this article in the departmental 'useful literature' file. This filing system is unlikely to succeed unless it is clearly one individual's responsibility and that should be at fairly senior level.

However, we are on the brink of the breakthrough in data retrieval which has had the Medline searches and now the CD ROMs as forerunners. When the computer terminal is as familiar and essential an item on the desk in consulting room and ward alike, we will be able to access up to date original articles and learned reviews at the touch of a few buttons. I can foresee the time when as the medical details (plus accounting data) is entered into the consulting room computer an automatic search will be made for relevant new literature on that child's condition. A summary of this will be available for inclusion in the word processed report that will be available for any of the child's professionals to access, as well as for inclusion in the hardcopy that the parents will be carrying. So the medical library will pass into the mists of memory as the stockmarket runners have and as the filing rooms in hospital will.

GRAHAM CLAYDEN
Reader in paediatrics

A Paediatric Vade-Mecum. 12th Ed. Edited by Jack Insley. 12th Ed. (Pp 296; £13·95 paperback.) Edward Arnold, 1990. ISBN 0–340–52693–9.

Who needs a Filofax when he can have the vade-mecum? This remarkable little book must have a greater concentration of paediatric data, in terms of facts per cubic centimetre, than any equivalent volume. This 12th edition has built on the proved worth of its predecessors by the addition of a chapter on resuscitation and by extensive refurbishment of other sections. It now covers most paediatric emergencies, infections and immunisation, neonatalogy, nutrition, fluid and electrolyte treatment, prescribing, investigations, developmental paediatrics and sundry other topics, all in the space of 300 pages. This is achieved by a condensed but careful layout on good white paper, though in places the print is so small as to tax the presbyopic. Nearly 30 contributors are listed—an impressive parade of the paediatric talent of Birmingham. The multiplicity of authors results in variations of approach, some favouring a more discursive style but only a few giving references. The scope of the book is vast but the depth is variable, reflecting the expertise and influence of each author. Some sections are rather sketchy, and others are more detailed and academic, sometimes well beyond the needs of the busy doctor in a general hospital.

A book that is such a 'Jack of all trades' cannot hope to master them all with equal success. The section on prescribing is particularly good with drug dosages set out with space and clarity. The sections on neonatology and developmental paediatrics, however, are so condensed that a person working in these areas would also need a more specialist text. Indeed one wonders if the cursory outline of developmental paediatrics sits happily in what is basically a 'hospital' book. The new house officer will look in vain for guidance on procedures, a common source of anxiety for the newcomer to paediatrics, but once the drip is up he or she can find a wealth of advice on what to put through it. The chapter on nutrition contains much useful data and good sense. The list of voluntary organisations and the advice on cot death add some humane leavening to an essentially clinical loaf. The brief section on burns could be improved by inclusion of a percentage chart for surface area and a firmer recommendation for analgesia. One important point that might be questioned is the definition of a glucose concentration of 1·5 mmol/l as the threshold for intervention in neonatal hypoglycaemia, which in the light of recent research is surely too low. There is also confused advice on pertussis immunisation together with an outdated schedule—the new one was introduced just as the book went to print.

Inevitably such a wide ranging book has points one can quibble over; however, the general standard of information and advice is excellent. The vade-mecum is a bargain at £13·95. Its portability is less relevant where white coats are not the fashion, but puts lady doctors with handbags at a definite advantage.

C J BACON
Consultant paediatrician

A Longitudinal Study of Adolescent Growth. By John M H Buckler. (Pp 450; DM 360 hardback.) Springer-Verlag, 1990. ISBN 3-540-19569-6.

Elephants and turtles (seagoing, not teenage mutant) take longer to reach maturity than man. As a consequence, adolescence in these animals is not well documented. Even so, few of us have the courage, long term confidence, and dedication to document, in large numbers of children, the relatively shorter period required to reach human maturity. Those that do succeed in such a task find their results providing reference data against which other individuals and other groups are matched. This book provides just such descriptive data on more than 300 children from secondary schools in Leeds, and a boys' public school in Berkshire, who were examined and measured three times a year between the ages of 10 and 18. The children were not randomly selected. The data are not complete in that prepubertal or late pubertal growth is missing for children who matured early or left school early. But these limitations are offset by the variety of anthropometric detail presented, the longtitudinal nature of the study, and, most impressive of all, the fact that the measurements were all taken by one observer—the author.

The book is constructed as a thesis. The chapters present various aspects of the study and discuss the findings and then present the relevant tables and figures. Over 150 pages at the end of the book are devoted to computer printouts of the centile distributions of measurements for the different groups of children. The rest of the book contains more pages of figures and tables than text. Thus this is not a book from which to learn the basic facts of adolescent growth for the Membership but an essential reference work for paediatric libraries, those with auxological aspirations, and as an armchair book for the seasoned growth expert who can compare Buckler's findings with his or her own interpretations of adolescent growth.

The wealth of figures and tables may make the book sound heavy going but in fact it is easy to read. Interpretations of the anthropometric findings are expressed clearly and concisely and the figures are drawn in such a way that other growth curves can readily be matched against them.

The wide spectrum of anthropometric change presented in this book leaves an overwhelming impression of the variety in adolescent growth which inevitably becomes fudged in cross sectional studies. This impression is enhanced by the discussion comparing the Buckler children with other studies. What rules does nature follow to determine growth when individual variation is so great? This reader longed for the extra dimension of parental size in the study. Adolescents wishing to achieve an ideal size must, I suspect, do one thing they could never do: choose their parents wisely.

ELIZABETH POSKITT
Senior lecturer in child health

Childhood Epilepsies: Neuropsychological, Psychosocial and Intervention Aspects. Edited by Bruce P Hermann and Michael Seidenberg. (Pp 264; £26·95 hardback.) John Wiley and Sons, 1989. ISBN 0-471-91270-0.

After an initial, orientating overview of childhood epilepsies (Dreifuss) this book comprises an interesting collection of chapters reviewing facets of the other side of epilepsy.

All the contributors are American apart from the authors of a rather familiar chapter on the effects of anticonvulsants on cognitive function (Cull and Trimble), and there is an essay by David Taylor demonstrating psychosocial components are no less important because they are difficult to measure.

The transatlantic differences in financial priorities revealed by some chapters are so great as to form their main impact and Britain does not do well by the comparison. The chapter on clinical monitoring introduces the child clinical neuropsychologist as a primary resource (Berent and Sackellares). Another on school performance suggests regular standardised psychometric assessments of children with epilepsy (Seidenberg). While 'vocational and psychosocial interventions for older adolescents' (Fraser and Clemmons) indicates a major difference in the allocation of funding in response to public laws.

The government paper proposing regional epilepsy centres remains but a dream for most of Britain, a dream resurrected at several points by this book, particularly by a final description of the comprehensive multidisciplinary inpatient unit for children with epilepsy in Charlottesville (Santilli and Tonelson). 'Behavioural approaches to management' (Schotte and DuBois), concentrates on compliance and mentions low cost medication containers with built in alarms that signal the times at which doses are to be taken (for example, the Electric Pill Box Timer, Alaron Incorporated). Behavioural strategies for the reduction of seizure rate are covered in only three pages which is disappointing. 'Epilepsy and mental retardation' (Zielinski) reviews its topic competently but seems to have strayed into this neighbourhood from another book.

There is a concise and helpful review of surgical treatment (Wyler) and an updated account of the cognitive prognosis for children with uncomplicated epilepsy (Rodin). A masterly summary of information processing in petit mal epilepsy by Mirsky describes interictal and preburst deficits and was for me the highlight of the book. A middle collection of three chapters, largely reporting local work, was less rewarding.

Many British children with epilepsy get rather a bad deal despite the efforts of their physicians.

It is easy to become tolerant of services as they are. There are not many ideas in this book that could be implemented without more money. Even if money was available, one might not wish to follow all of the paths trodden here.

M PRENDERGAST
Consultant child psychiatrist

Developmental Speech Disorders. Edited by Pamela Grunwell. (Pp 200; £19:95 hardback.) Churchill Livingstone, 1990. ISBN 0-443-03992-5.

Problems with speech and language development are the commonest problems encountered in the preschool population and for many will have long term implications. During the last 20 years there has been remarkable progress in applying the sciences of cognitive neuropsychology and linguistics to clinical practice. Our methods of looking at language development have during this time concentrated on the development of hierarchical linguistic subdivisions of language, for example semantics and phonology. It is likely that in the future there will be a greater concentration on how these different areas are linked and integrated, and the assumed psychological reality of those theoretical categories will be challenged, for example Bates *et al.*[1] Pamela Grunwell has edited this multiauthor book for a range of professionals interested in language and speech problems with the aim of setting current clinical practice within a theoretical framework.

Section I with chapters by Grunwell and Hewlett sets the theoretical framework. For any theory to have validity it should be able to account for normal development with its acquisition of a rule based system and also for pathologies, which extend from difficulties associated with deafness, including the child who cannot articulate because of bulbar involvement, and the child who has superbly imitated speech and is frequently hyperlexic but where the link to cognitive meaning is defective. For the non-speech pathologist, the terminology of linguistics can be confusing. The terms phone, phoneme, and phonology have precise definitions within theoretical linguistics and when their use is extended to clinical problems and psycholinguistic processes, they need to be used consistently within those definitions, or redefinitions should be explict and justified.

Several chapters redraw the boundaries between terms. If 'phonology' is the set of linguistically relevant speech sounds, then it is reasonably consistent and clinically useful to use 'phonology' also as being the contrastive use of speech sounds. However, for others here 'phonology' includes 'meaning', yet meaning is separated from phonology in general linguistics, and in cognitive neuropsychology semantic meaning can be dissociated. Hewlett sets out his version of the cognitive neuropsychology model of input and output lexicons and suggests an interesting pathway for the development of automaticity and speech output pathology.

There is a lot of recent research on the early development of vocalisations and the transition between this and babble (which can be precisely defined as reduplicative 'CVCV' utterances—a period of motor rehearsal of phonemes) which is influenced by the phonetically contingent responses of the adult (adding meaning in communicative context is another dimension).[2] Hewlett specifically stated (p 18) that he was omitting extensive discussion of this early stage and the influences upon it, but for alert parents and clinicians it may be an early sign of pathology and is of great theoretical interest.

There is little or no mention of prosody and its development and theoretical relationship to phonology, although it is discussed in the clinical problems section where it is clear that problems of prosody frequently coexist with phonological problems. Placing specific developmental phonological disorders in the context of other language disorders is dealt with in chapter 7 where many theoretical points are made which might have come earlier in the book. The section on 'dyspraxia' makes clear that this complex clinical problem often includes difficulties beyond the 'motor programming' of speech sounds but it remains a term used clinically in different ways by different people. Apart from Hewlett's model of output, I did not gain a clear view of the relationship of theory to clinical problem and consequent logical therapeutic intervention.[3]

In Chapter 3 Howell and McCartney opt for a cognitive approach to active learning along the Piagetian model in their treatment strategy. They stress the importance of assessment to try to define the level of difficulty but point out that in a child with a disorder there may be several levels of difficulty and one additional problem may be integrating several aspects of linguistic development and language use. In general this was a useful chapter, although it would have been helpful to have this linked to the chapter on specific developmental language problems.

Sections II and III of the book include practical accounts of assessment and management of speech disorders in orofacial abnormalities and deafness. These chapters are well written and, together with a very good chapter by Joy Stackhouse on reading and spelling disorders, will be useful guides to clinical practice.

Finally, what are the effects of a severe speech difficulty on language and especially phonology development. This complex relationship is discussed on p 140 and further studies by Bishop have thrown light on this area.[4]

In conclusion, there are some excellent chapters which make stimulating reading but for this reader the aim of setting clinical practice in a coherent and consistent theoretical framework was not entirely achieved.

GILLIAN BAIRD
Consultant paediatrician

1 Bates E, Bretherton I, Snyder L. *First words to grammar*. Cambridge: Cambridge University Press, 1988.
2 Stoel-Gammon C. Prespeech and early speech development of two late talkers. *First language* 1989;9:207–24.
3 Dodds B, Leahy N, Hamble G. Phonological disorders in children. *British Journal of Developmental Psychology* 1989;7:55–71.
4 Bishop D, Mogford K. *Language development in exceptional circumstances*. Edinburgh: Churchill Livingstone, 1988.

Pediatric Trauma. Proceedings of the Third National Conference. Edited by Arnold G Coran, Burton H Harris. (Pp 248; $49:50 hardback.) J B Lippincott Company, 1990. ISBN 0–397–51108–6.

As the majority of paediatricians appear to have little interest in the commonest cause of death and disability of children in the developed world, a dip into this book may serve as an introduction for the uninitiated.

The book is a compilation of the major lectures given at the Third National Conference on Pediatric Trauma in Michigan in September 1989. The lectures aimed to highlight major clinical and experimental advances rather than to be a comprehensive view of the field of paediatric trauma. However, it seems a pity that there is not even one chapter on head injury, which is the commonest overall cause of death and permanent handicap after injury.

Chapters are largely divided into four groups. Firstly into those on the organisation and economics of paediatric trauma care, which although relating to US health economics systems and the geography of a continent, make intriguing reading. The second group of chapters on clinical and experimental shock is too condensed and poorly referenced for real discussion of a complex topic. In the section on the clinical management of shock, I was surprised to see no mention of the intraosseous route for venous access. Chapters on the management of abdominal trauma were however, illuminating, presenting a lucid and balanced discussion of the clinical problems as well as being well referenced. Finally, there are a group of chapters on accident prevention including a useful discussion of car restraints for infants and children. The book concludes with a thumb nail sketch of children's accidents in South Africa.

In this country we have no 'trauma surgeons' and injured children may be treated in a wide variety of specialities. Although trauma is a surgical disease, there could be a role for paediatricians at various stages of treatment.

Who should buy this book? It should appeal to a wide audience of surgeons, accident and emergency specialists, and paediatricians. However, it is not a definitive textbook and will doubtless be superseded by the proceedings of the Fourth National Conference on Pediatric Trauma in a couple of years. I would persuade your hospital librarian to buy a copy for general use rather than investing in it personally.

BARBARA M PHILLIPS
Consultant paediatrician,
accident and emergency department

Pocket Atlas of Pediatric Ultrasound. C M Rumack, J G Horgan, T C Hay, and D Kindsfater. (Pp 118; $18 paperback.) Raven Press, 1990. ISBN 0–88167–620–9.

'This pocket atlas will be useful for all students beginning radiology studies and will serve as a guide for all ultrasonographers who rarely see children and need to know what is normal'. . . concludes the preface to this slim volume.

The authors have compiled an atlas of eight anatomical sites. These range from the mundane (brain, liver, kidney) via the intermediate (hip, cerebral Doppler) to the esoteric (spine). The format involves unlabelled sonographs in standard section accompanied by a labelled shaded diagram of the sonographic image and a useful anatomical diagram of the scanning plane.

The quality of the sonographic images is extremely variable. Several of the images of the brain sections and most of the renal and adrenal scans are excellent. In contrast, the liver/pancreas scans are of indifferent quality and the hip scans are particularly obscure. The labelling is for the most part accurate, although I noted two factual errors in the echogenic central spinal canal. Recent work has shown this feature to be the image of the interface between ventral white commisure and the anterior median fissure. More imporantly, the transverse hip scan identifies the actabular labrum as a lucent space. The labrum is composed of echogenic fibrocartilage and the structure indicated is actually the unossified hyaline cartilaginous acetabular roof, a landmark of paramount importance to the European approach to hip ultrasound.

Accuracy notwithstanding, is this a useful book? Personally I feel that ultrasound cannot be taught or even described in a vaccum, which this book is attempting to do with its absence of text and normal variants. It is essential that a paediatric ultrasonologist be aware that infant renal papillae are occasionally mistaken for dilated calyces and that the interenunchal junction (not described) is not an upper pole renal scar. In the same vein I see no point in including examples of cerebral Doppler examinations unless it is to inform the reader of the feasibility of such an examination. Returning to the concluding statement of the preface, surely the authors are not suggesting that ultrasonographers 'who rarely see children and need to know what is normal', would when equipped with this volume be able to perform and more importantly interpret paediatric studies. The practitioner who finds this level of description novel and informative should, in my opinion, have the insight not to be performing unsupervised paediatric ultrasound examinations.

L BERMAN
Radiologist

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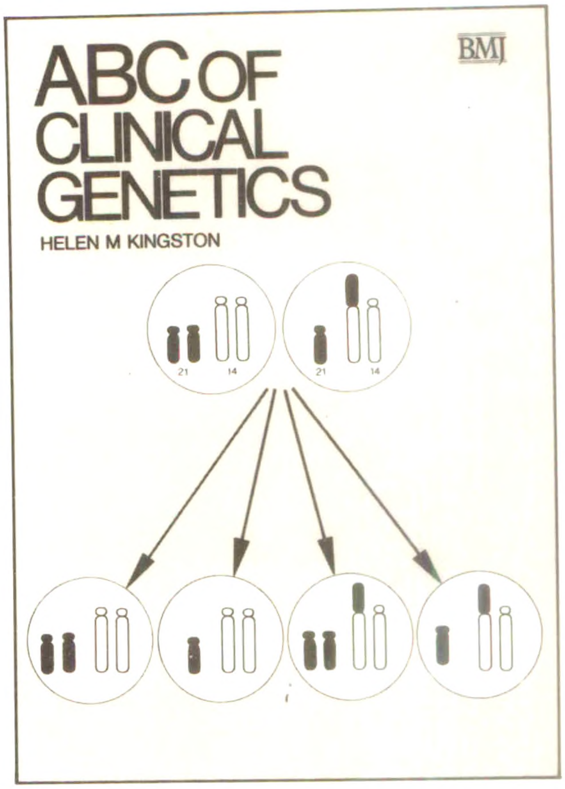

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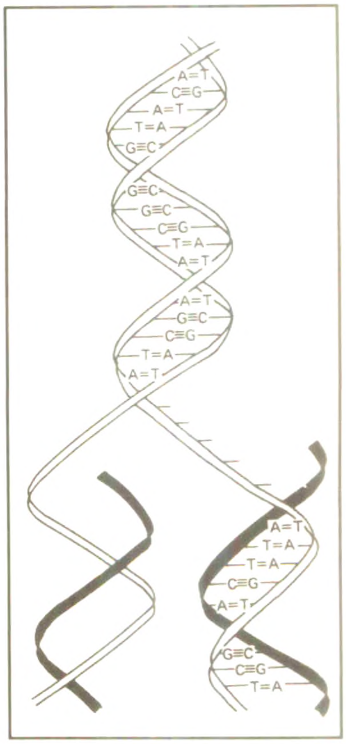

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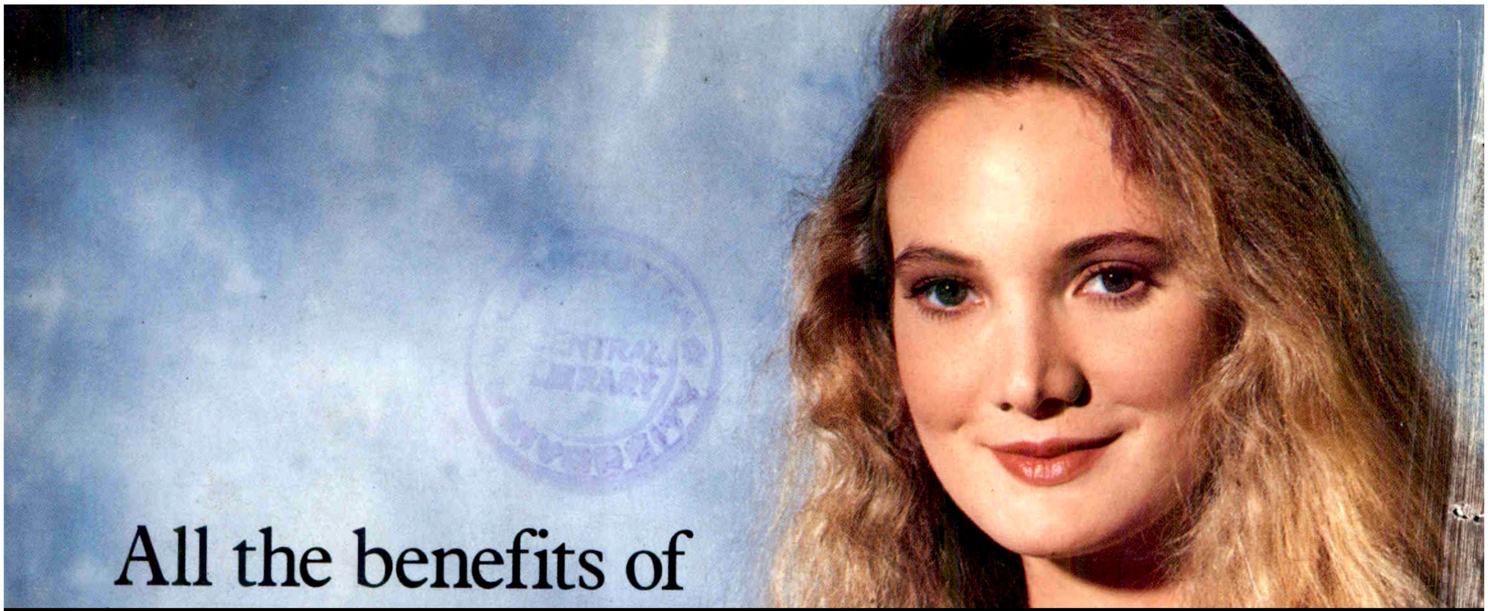

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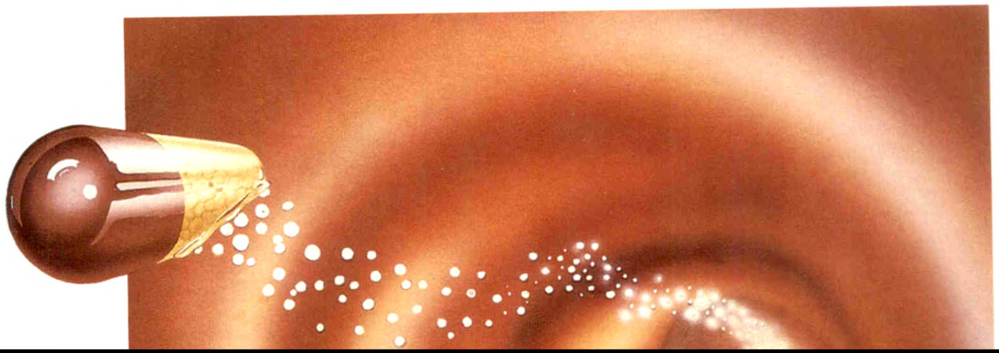
In The Management Of Cystic Fibrosis



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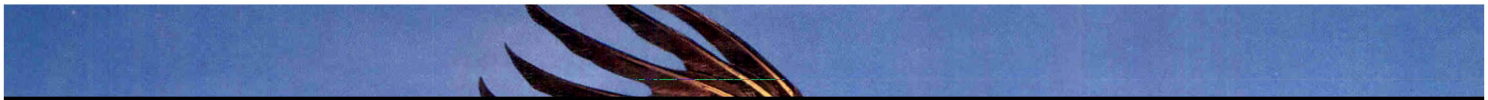

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The Journal of the British Paediatric Association

Annotations

Implications of the Children Act for paediatricians

The Lord Chancellor has stated that the Children Act, which will be implemented in October 1991, represents the biggest reform of law relating to children in living memory. The extent of the change involved is perhaps reflected by the fact that altogether 35 consultation papers will be issued by the Department of Health. To date most of the papers relating to the first phase of consultation have been distributed and the resulting comments will, no doubt, be incorporated in the final regulations and guidance expected early in 1991. Unfortunately the period of time allowed for response became shorter with each batch of papers and this may result in feelings of frustration and discontent.

Paediatricians in general, however, will welcome any changes that make child care law easier to understand and, more importantly, promote and protect the welfare of children. So it is worth exploring some aspects of the act more closely. Many introductory guides have been published. The HMSO publication[1] and the National Children's Bureau training pack[2] provide very useful overviews but paediatricians should avoid 'dipping in' if they are to appreciate the full flavour of the act.

The welfare principle

The welfare of the child is paramount. No court order will be made unless it is clearly beneficial to the child and a checklist is provided to assist in these deliberations. Most of the items on the list are not new but emphasis on the consideration of the wishes and feelings of the child is welcome.

Parental responsibility

Paediatricians are in regular close contact with parents and their children and already possess well developed 'partnership' skills. The promotion of parental responsibility rather than parental rights will be supported, but paediatricians will have to remember that both parents retain that responsibility after divorce and when their child is being 'looked after' by a local authority.

There is widespread concern that parental interests are not being sufficiently considered. Parental participation at child protection conferences honours the spirit of the act but is viewed less than enthusiastically by many paediatricians.

Children in need

A child is considered to be in need if:

- He or she is unlikely to achieve or maintain, or to have the opportunity of achieving or maintaining, a reasonable standard of health or development without the provision of services by a local authority;
- Health or development is likely to be significantly impaired, or further impaired, without the provision of such services;
- He or she is disabled.

Each local authority is required to take reasonable steps to identify these children, to provide appropriate services to meet their needs, to promote care within the family, to publish information about the services, and to ensure it is received. The local authority is required to keep a register of disabled children and may make an assessment of need linked to assessments under other legislation—for example, Education Act 1981, Disabled Persons Act 1986. From these requirements flow many implications for paediatricians.

The definition of 'in need' is open to interpretation hedged as it is with words like 'reasonable' and 'significant' and as a term is potentially divisive.

All children should have access to services designed to promote their health and development. As the implementation of the act will take place with no increase in resources, will disadvantaged children have to receive support at the expense of other children? Can it be said with total certainty which services will definitely promote health and development? If not, will that lack of certainty justify a limited provision as no guarantee of improvement is forthcoming? There is therefore understandable concern that resource restraint will result in a limited definition of 'in need' in order to reduce demands on services.

How will children in need be identified? A significant number will be known to the professionals who deliver preschool child health surveillance programmes and the school health service.

Greater attention will now have to be given to children who 'miss out' on surveillance, homeless and travelling families and non-attenders, and consideration given to a more selective approach. Specific groups of children in need include those in care, on child protection registers, and with educational problems.

The definition of disabled will jar with paediatricians but it is the one used in the National Assistance Act 1948 in respect of adults. Entry to the register, which the local authority is required to keep, is voluntary but paediatricians will be familiar with the reluctance of many parents to have the names of their children on handicap registers. Though confusion with child protection registers must be avoided, reassurance will grow if benefits from registration can be demonstrated. Registers relating to many of these children already exist. The community child health service usually maintains a more widely based special needs register that serves to facilitate clinical care and management. The education authority has a register of children with special educational needs. Clearly it would be undesirable to design another separate system to meet the requirements of the act.

The identification of children in need and disabled children in particular will require close collaboration between health, social services, and education agencies. Procedures whereby information is shared will have to be carefully designed. If they are to be effective more accurate and accessible information systems will have to be developed. Children move in and out of the category 'in need' so the exercise of identification will have to be kept under regular review. To facilitate an integrated approach a common health pathway will have to be established in each health district. Many local authorities will look to the community child health services for an adviser in this matter. Whoever is ultimately identified will need time designated to meet the commitment and adequate administrative support.

Care orders

The act clearly states that compulsory intervention must be fully justified. Care and supervision orders will require demonstration of 'significant harm'. Harm is defined in the act and consists essentially of a deficit in or detriment to the standard of health, development, and well being that can reasonably be expected for the *child in question*. The court will have to decide what is 'significant' and will be able to draw on expert advice. Paediatricians, among others, can be expected to be involved in this advisory process. In order to do so they may need training in order to draft clear, accurate reports and advice about presentation in court.

The status of voluntary care will be abolished. A child will be 'looked after' when in the care of a local authority or when provided with accommodation, which may be in a foster home or children's home or some other appropriate arrangement. A higher profile is given to identification of the health and developmental requirements of these children, many of whom will come into the children in need category. Many local authorities already rely on a medical adviser, frequently recruited from the community child health services, to coordinate identification of needs. Good practice such as this will be expected on a more regular basis and will have resource implications for paediatricians.

Child protection

The Children Act introduces new protection orders that also have implications for paediatricians. An *emergency protection order* will replace a place of safety order. It will be made when there is reasonable cause to believe that the child is likely to suffer significant harm if not made 'safe'. The court can give directions for a medical or psychiatric examination or other assessment. As the order can last for only eight days and be extended only once for a further seven days, health agencies will have to be able to react promptly.

Under a *child assessment order*, which will last for seven days, a court can authorise a health or developmental assessment. The order will be able to specify what is to be done, when the assessment should start, and who should do it. Again, the health professionals involved will have to be reactive, possibly at the expense of other commitments.

Under all these orders a child with sufficient understanding to make an informed decision can refuse to undergo an examination or assessment.

Money from central government has been made available to promote training programmes about the act within social services departments. Regrettably this has not been so for doctors, although individuals have benefited from multidisciplinary training opportunities organised at local level by social services departments. There is still time for this deficit to be corrected.

Assumptions have been made that there will be no significant health resource implications flowing from implementation of the act. Clearly from what has been discussed above this is not true. Even if health agencies wanted to restrict their contributions, it would not be possible to do so as Section 27 of the Children Act allows a local authority to request help from a health authority. Having received a request that authority must comply.

As the act provides an excellent opportunity for better service planning between social services, health, and education, paediatric services will be eager to participate. Coordination of the health participation should be easier in those districts where an integrated child health service has been introduced. Other districts where integration has been rejected or fleetingly discussed could take the opportunity to reconsider their decision.

In all circumstances the health resource implications of implementation of the act must be acknowledged and accommodated within the purchaser and provider plans currently under consideration. Similarly relevant, and possibly new, sevice commitments should be identified when contracts for consultant paediatricians are agreed.

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1 Department of Health. *An introduction to the Children Act*. London: HMSO, 1989.
2 National Children's Bureau. *Working with the Children Act*. London: NCB, 1990.

See related article on p536.

Social and emotional impact of childhood asthma

Recent research suggests that asthma morbidity in children is on the increase.[1] This is particularly worrying in the light of evidence that asthma is often poorly managed both by general practitioners and in hospital.[2 3] Patients and their carers, for their part, have been criticised for failing to comply with prescribed treatment or to manage attacks appropriately.[4] Not all the problems, however, are due to poor management: for some patients, asthma can be very difficult to control.[5 6]

Any disease is likely to have some impact on the social and emotional lives of sufferers and their carers. That impact may be greatest where symptoms are not adequately controlled. But even the underlying presence of disease can cause distress and concern. Prevention, avoidance, and management strategies can themselves create difficulties in people's everyday lives. It is also important to recognise that, although sufferers and carers may sometimes claim to lead 'normal' lives, such 'normality' may be based on adjustments and restrictions that they have already incorporated into their lifestyles: their redefinition of normality enables them to emphasise the positive aspects of those lifestyles and avoid focusing on any underlying problems.[7]

In the case of children and their families, the social and emotional impact of asthma can be subdivided into four main categories: social and leisure pursuits, schooling, practical aspects of daily life, and emotional effects.

Social and leisure pursuits

The extent to which asthma affects children in their social and recreational activities largely depends on how well their symptoms can be controlled. Although some studies suggest that children experience few difficulties in these areas,[8] others highlight the problems that some children do suffer.

Asthma can, for example, affect the ability to take part in sport. In one study, 61% of the parents of asthmatic children said their children's participation in sporting activities was restricted.[9] Elsewhere, 22% of a sample of 111 children with asthma had been advised to avoid some sports, 25% had at times been unable to complete a game involving exertion, and 39% had occasionally missed sport due to their asthma.[4]

Some children have to avoid coming into contact with animals: one study of asthmatic children found that 20% of families had to get rid of pets.[8] The need to avoid pollen and smoke may similarly restrict children's play and leisure activities. Holiday arrangements can be affected: in one study, 57% of families reported some degree of restriction[9]; in another instance, some families were prevented from going on holiday at all.[10]

In addition to having an impact on the child's own life, asthma can thus affect the social and leisure pursuits of the family as a whole. Siblings may be affected because of restrictions on the asthmatic child. And parents may be prevented from going out in the evenings or enjoying a life of their own.[10]

Schooling

Asthma is the most common reason for children's absence from school.[11] One study found that, since starting school, one in three 7 year old children who suffered from asthmatic symptoms had missed more than 50 days' schooling as a direct result of asthma: this represented more than three times the usual number of absences.[12] It is in their early years that children with asthma miss most days' schooling[13]: younger children are more likely to pick up respiratory infections which precipitate attacks.[14] But another study found that half of a sample of severely asthmatic children aged 10 to 15 also experienced serious disruption to their education as a result of acute attacks.[13]

School absence can affect academic performance, and frequent short absences are generally more harmful in this respect than an occasional long one.[15 16] School absence can also lead to psychological problems as a result of the child feeling different or inferior or being overprotected. These problems can in turn exacerbate the symptoms of asthma.[17] The association between asthma and school absence, however, is not straightforward. One study found that school absence among asthmatic children was associated with parental separation, the non-manual occupation of the mother, having three or more children in the household, poor maternal mental health, lack of access to a car, and living in rented accomodation.[8] Although the authors of this study did not attempt to ascribe any causal explanations for school absence, their findings did suggest that social circumstances and psychological factors play a part in determinig whether children with asthma stay off school.

Within school itself, some children experience problems if they have to undertake activities that provoke attacks or—equally inappropriately—if they are not allowed to participate in normal physical activities.[17] Such problems are clearly exacerbated where schools do not allow children to use asthma medication.[17]

Practical aspects of daily life

Depending on the specific factors which provoke attacks, children may have to avoid particular foods, stay away from dusty or smoky environments, and be protected against catching colds insofar as this is practically possible.[11 14] Parents are often advised to remove carpets, soft furnishings, and soft toys from bedrooms—even though this may remove an atmosphere of normality from the bedroom and deprive the child of sources of pleasure and comfort.

Parents of asthmatic children are often faced with extra housework in the form of additional cleaning, dusting, and washing in order to reduce exposure to potential irritants. Nocturnal attacks mean that parents will lose sleep and be physically exhausted.[10 18] Parents may have to take time off work or give up their jobs; this can cause particular difficulties for one parent families.[10 19 20]

Asthma can also involve financial costs. These result from time lost from work, transport to surgeries and hospitals, babysitter costs for other children (while the asthmatic child is at the hospital or surgery), and special purchases such as air cleaners, humidifiers, or special bedding.[21] A study in the United States found that low income families bore a relatively greater financial burden, with an average of 1·5% of their income being spent on indirect costs.[21] In one case, such costs amounted to 6·3% of the family income. If carers have to give up work altogether, serious financial problems can occur.[7 10]

Emotional effects

Chronic illness can cause stigma, a loss of self esteem, and family strain.[22] In one study, 41% of parents of asthmatic children said that asthma caused their children to feel self pity; 21% reported that their children had a poor self opinion, and 23% felt their children had poor relationships with their peers.[9] It is certainly the case that restrictions on social activities can increase a child's sense of isolation and create further difficulties in establishing social contacts.[15]

Asthma can also have a major impact on family life. Parents of asthmatic children have stated that the asthma is 'a constant worry' for them, leaving them in a constant state of 'red alert' and unable to relax, even when the asthma is essentially under control.[10 14 20] The emotional strain can be considerable: 34% of parents in one study felt that their child's asthma had an adverse effect on their own (parental) relationship.[9] Parents may also feel a sense of guilt, whether or not this is justified: they may, for instance, feel they are to blame for their child's susceptibility to asthma attacks.[7]

In some cases, anxiety on the part of the parents of asthmatic children can lead to over protectiveness and/or to a failure to exercise adequate discipline.[23] Where family life is centred around the asthma, this can create a sense of oppressive closeness for the child.[18] It can also mean that other children receive less than their fair share of parental attention: some parents feel it is often the other children who suffer most.[14] In other instances, the fear resulting from observing the symptoms of asthma, and an awareness of its potential consequences, can cause the families of asthma sufferers to deny the existence of the condition and to pretend it does not exist. Such families will find it hard to offer sufferers any support or comfort and may instead become hostile and accuse the sufferer of manipulation.[23]

Children, for their part, may react to their asthma by using it to seek attention or avoid unpleasant activities.[20] Some children have been reported to be able to play football at school while claiming to need a wheelchair at home.[18] In some instances, parents have felt totally unable to control their child's 'tyranny' and physical aggression and have only obtained help through psychiatric intervention.[24]

It should be recognised, however, that asthma does not always or only have negative effects. Many parents have found that asthma has brought their families closer together and that they now undertake more activities together.[9 20]

Conclusions

Although treatment for asthma has improved considerably over the past 30 years, many sufferers and carers continue to experience problems in their everyday lives. This may in part reflect the difficulty of fully controlling the disease; further work is certainly needed to examine the precise relationship between symptom control and social and emotional problems.[25]

In the meantime, parents state that the impact of asthma on themselves and their children is seldom fully recognised.[7] They often encounter scepticism or incredulity when they describe their problems; indeed, they are often blamed for causing those problems themselves. A better appreciation of the social and emotional impact of asthma is essential if children and their families are to receive the care and assistance they need.

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Hyperexplexia or stiff baby syndrome

The stiff baby syndrome or hyperexplexia is an unusual neurological disease, occurring via dominant autosomal transmission, and distinguished by a permanent hypertonia that is heightened by the slightest stimulus. The diagnosis can further be ascertained by the clinical and electromyographic aspects, as well as the occurrence of a family history. The evolution of the disease is benign with myorelaxing treatment. The recognition of this syndrome is of great importance in order to avoid an erroneous diagnosis of epilepsy, to warn the parents against the risk of recurrence in case of later pregnancies, and to indicate the necessity of constant supervision during the neonatal period as attacks of hypertonia may lead to apnoeas that can endanger the child's life.

Hyperexplexia was described for the first time in 1962 by Kok and Bruyn in 29 members of one family.[1] The disease was characterised by the occurrence of a hypertonia from birth, which became less pronounced during the first year of life but could later lead to repeated falls. Those characteristics were later reported by Suhren *et al* on 25 members of a family.[2] In 1972, Klein described a family of 10 who presented with a syndrome distinguished by attacks of hypertonia heightened by the slightest physical stimulus and in whom an electromyogram showed a persistant activity even on resting; this activity vanished on treatment with diazepam [3] In 1981, Lingam *et al* described the same symptoms and named the disease: stiff baby syndrome.[4] Another case was reported by Melki *et al* in 1988.[5] In all cases a muscular stiffness appearing from birth is reported, which gives the child a peculiar attitude described as 'fetal', and there is a flexion of the forearms and legs and closed fists. The expression of the child is also characteristic: the stare is fixed and gives the child an expression of anxiety. The hypertonia diminishes during sleep but increases with the slightest psychic or tactile stimulus. Attacks of hypertonia can involve respiratory muscles and lead to apnoeas, endangering the child's life. Digestive troubles, such as vomiting, are also reported. Vomiting is, in most cases, in association with a hiatal hernia. It is also noted that umbilical, inguinal, and diaphragmatic hernia are more frequent; they are attributed to the hypertonia.

Electroencephalography is normal but electromyography gives a characteristic result and shows an almost permanent muscular activity with, however, periods of electric quietness.[6] The nerve conduction velocity is normal. The evolution of the disease is characterised by a delay in reaching motor 'milestones' (for example, walking). The hypertonia is reduced during the first two years, but abnormal reactions such as involuntary starts remain after the slightest stimulus. There is neither mental nor neurological deficiency.[7]

It is important to distinguish the stiff baby syndrome from other neurological diseases manifest by an increase in muscle tone. First, this syndrome must not be confused with the stiff man syndrome described by Gordon *et al* in 1967.[8] The stiff man syndrome is not hereditary and appears at the age of 40 to 60; evolution is slow and progressive. It is distinguished by a permanent contracture, an intense dysphagia, the electromyogram shows a permanent electric activity, even during rest, and it is magnified by the slightest tactile or nociceptive stimulus.[9] The Isaacs-Mertens syndrome, usually occurring around the age of 30, and for which neonatal forms have been reported, presents a mostly distal hypertonia, accompanied by fasciculations; the electromyogram shows a permanent activity on resting as well as numerous discharges. The syndrome described by Stevens in 1965 under the name 'Jumping Frenchman of Maine' is different, as violent starts, produced by the slightest stimulus, are associated with an echolalia and an echopraxia.[10] Gilles de la Tourette's syndrome chiefly presents spasmodic twitchings and startling reactions. Several other conditions can produce abnormalities in tonicity: among them are the encephalomyelites, Creutzfeldt-Jakob disease, metoclopramide or strychnine poisoning, and myoclonic epilepsy.

The physiopathological mechanism of hyperexplexia is controversial: Markand thinks that the hypertonia is linked to a hyperactivity of cortical neurons,[11] but Suhren *et al* and Morley *et al* invoke an abnormality in the inhibitory system of the brain stem.[2 12] Andermann *et al* think that the problem is with the serotoninergic system.[6] Myorelaxing treatments such as diazepam are efficient as they enable a lowering of the hypertonia. There can be a reappearance of the symptoms when the treatment is stopped to carry out electromyography.

The recognition of the stiff baby syndrome is of great significance in order to avoid an erroneous diagnosis of epilepsy and consequent treatment with anticonvulsants. Recognition is also important so that treatment with myorelaxants can be started to avoid the abnormal startle reactions that produce falls in older children. It is also important to warn the parents about the risk of reccurrence of the disease, and to indicate the necessity of constant supervision during the neonatal period, as attacks of hypertonia can lead to serious apnoeas endangering the child's life,[13] although the evolution of the disease is benign when treated.

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ORIGINAL ARTICLES

Importance of 6-mercaptopurine dose in lymphoblastic leukaemia

J P Hale, J S Lilleyman

Abstract

To explore the possibility that higher total dosage of 'maintenance' treatment may have contributed to the recent improvement in outlook of children in the United Kingdom with lymphoblastic leukaemia, details of the amount of 6-mercaptopurine prescribed during the first two years of treatment were studied in an unselected cohort of children diagnosed between 1973 and 1987. Eighty five patients were studied, 30 diagnosed before and 55 after 1980. The group diagnosed after 1980 showed an 18% improvement in relapse free survival at five years. Their median total dose of 6-mercaptopurine had increased by 22%, whereas according to the protocol it should have risen by an average of only 9%. After 1980 boys were prescribed significantly more 6-mercaptopurine than girls, and had fewer dose reductions because of myelosuppression.

These findings support the clinical impression that after 1980 an important therapeutic difference resulting from the new United Kingdom acute lymphoblastic leukaemia protocols was an increase in the amount of 6-mercaptopurine that children actually received as a result of changes in prescribing guidelines rather than dose. They also provide further evidence that boys tolerate 6-mercaptopurine better than girls, which may be related to the still unexplained difference in prognosis between the sexes.

During the last decade there has been a striking improvement in long term survival for children with lymphoblastic leukaemia in the United Kingdom.[1] Before 1980 treatment protocols were somewhat vague about what modifications in dose were permitted during the 'maintenance' phase of treatment, with the result that many clinicians veered away from doses that caused myelosuppression to minimise morbidity. With the implementation of the United Kingdom acute lymphoblastic leukaemia (UKALL) VIII protocol in 1980, which required a much greater degree of compliance by doctors to a strict regimen of permitted modifications in doses, two notable differences gradually became apparent. Firstly, there was an increased incidence of morbidity and mortality as a result of the treatment and secondly, despite this, there was a 20% improvement in long term survival.[1]

The two antileukaemic drugs that were most affected by the changes in prescribing practice were 6-mercaptopurine and methotrexate, both of which were used during the 'maintenance' phase of treatment. Of these 6-mercaptopurine was likely to be the most important as the dose of methotrexate was relatively small.

It is important to understand that the main differences between protocols before and after 1980 are related to adjustments in dose rather than 'target' protocol doses. Our hypothesis was, therefore, that children treated for acute lymphoblastic leukaemia since 1980 had been prescribed more 6-mercaptopurine by having the dose reduced less frequently and that this could be an important factor in their better prognosis. We also suspected that, based on preliminary work on the pharmacokinetics of 6-mercaptopurine,[2] there may be a difference between the sexes in tolerance of 6-mercaptopurine, and it was to explore these two suppositions that the present study was undertaken.

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Patients and methods

PATIENTS

Children with acute lymphoblastic leukaemia who were attending the Children's Hospital, Sheffield and who had completed two years continuing chemotherapy in their first remission were studied. The patients were divided into two groups, those diagnosed before 1980 (December 1973 to February 1980) and those diagnosed after 1980 (March 1980 to April 1990). In the group diagnosed before 1980 consecutive cases who received chemotherapy according to the Medical Research Council trial protocols UKALL III (arms 'ordinary' A, B, C, and D and 'ordinary modified' A and E)[3] and UKALL V (arms 'continuous' and 'gaps')[4] were studied. In the group diagnosed after 1980 children receiving chemotherapy according to protocols UKALL VIII (arms A and B)[1] and UKALL X (arm A) were studied. Only arm A of UKALL X was used because the effect on the outcome of treatment of the additional blocks of intensification treatment in arms B, C, and D of the trial was not known. Only children with no mediastinal mass and diagnostic white cell counts of less than $20\times10^9/l$ were eligible for UKALL III and V, so when comparisons were made between patients diagnosed before and after 1980, children with T-cell acute lymphoblastic leukaemia and white cell counts of more than $20\times10^9/l$ at diagnosis were excluded from the group diagnosed after 1980. When the group diagnosed after 1980 was studied on its own, children with all immunological types of acute lymphoblastic leukaemia (except B-cell) and all diagnostic white cell counts were included.

Medical Research Council trials in childhood acute lymphoblastic leukaemia

Trial	*'Maintenance' regimen of 6-mercaptopurine*	*Maximum cumulative dose of 6-mercaptopurine (mg/m^2) at eight 'maintenance' cycles*
UKALL III (ordinary A,B,C,D)	75 mg/m^2/day continuously from week 4	52 500
UKALL III:		
Modified A	25 mg/m^2/day, weeks 4–9 75 mg/m^2/day from week 13	51 450
Modified E	25 mg/m^2/day, weeks 4–9 75 mg/m^2/day from week 13 with one week gap every four weeks	34 650
UKALL V:		
Continuous	25 mg/m^2/day, weeks 5–8 50–70 mg/m^2/day from week 12	47 915
Gaps	25 mg/m^2/day, weeks 5–8 70–100 mg/m^2/day from week 12 with one week gap every three weeks	45 675
UKALL VIII (A+B)	75 mg/m^2/day from week 5	52 500
UKALL XA	75 mg/m^2/day from week 6	51 975

Children were studied from the time that they started receiving 6-mercaptopurine during the phase of treatment directed towards central nervous system prophylaxis and throughout eight subsequent cycles of 'maintenance' chemotherapy. All the protocols are described in detail elsewhere,[1 3 4] and the differences in 6-mercaptopurine regimens among them are shown in the table. All contained an induction phase of four to five weeks when they received weekly vincristine intravenously (1·5 mg/m^2), daily oral prednisolone (40 mg/m^2), and asparaginase (crisantaspase) intramuscularly, the doses and times varying depending on the protocol. UKALL VIII A and X also included two intravenous doses of daunorubicin (45 mg/m^2). Induction was followed by a central nervous system prophylaxis phase of two to three weeks during which cranial radiotherapy was given (24 Gy in UKALL III and V, and 18 Gy in UKALL VIII and X). This was accompanied by weekly intrathecal methotrexate, and 6-mercaptopurine was started during this phase. 6-Mercaptopurine was given as a single daily oral dose, the dose being dependent on the protocol. Treatment was continued either continuously (UKALL III 'ordinary' and modified A, VIII, X and V 'continuous') or with a one week gap every three (UKALL III modified E) or four weeks (UKALL V 'gaps'), together with weekly methotrexate orally (20 mg/m^2) and monthly vincristine intravenously (1·5 mg/m^2) with five days of oral prednisolone (40 mg/m^2). 'Maintenance' treatment was given for two to three years depending on the protocol.

In all the protocols the dose of 6-mercaptopurine was reduced if myelosuppression occurred. In UKALL III and V the aim was to keep the total white cell count at $2–3\times10^9$/l, but instructions were not specific and modification of the dose was largely at the clinicians' discretion.

In UKALL VIII and X much stricter criteria for modifying the doses of 6-mercaptopurine and methotrexate were introduced; the drugs were reduced to 50% or 0% of the target dose if the neutrophil count fell to less than 1 or less than $0·5\times10^9$/l. They were restarted when the counts rose above the threshold and built up to the target dose again over a period of three weeks.

In the latter part of UKALL VIII and throughout UKALL X oral co-trimoxazole was given during 'maintenance' chemotherapy. Children on UKALL VIII received the drug daily for the first 27 weeks, and those on UKALL X took it three times weekly throughout treatment.

PRESCRIBING OF 6-MERCAPTOPURINE

The actual amounts of 6-mercaptopurine prescribed for each child during central nervous system prophylaxis and the first 24 months of 'maintenance' treatment were extracted from the records. They were converted into mg/m^2 for each three month period and then added together. For those diagnosed after 1980 the longest uninterrupted period at the target dose and the number of times that the dose was reduced because of myelosuppression were also extracted.

This was not done for the group diagnosed before 1980 because few children were ever given the target dose and because there was no consistency in the degree of myelosuppression that led to a reduction in dose, so the results could not be compared.

STATISTICAL ANALYSIS

The Mann-Whitney U test was used to compare medians. Duration of remission between the groups was compared by the log rank test.[5] When considering control of the disease by treatment, deaths during remission and second malignancies were not counted as 'events' but were censored at the time of their occurrence.

Results

PATIENTS

In the group diagnosed before 1980 there were 30 eligible children (19 boys and 11 girls). Nineteen children were treated according to UKALL V (11 boys and eight girls), and 11 according to UKALL III (eight boys and three girls). The ages at diagnosis ranged from 2 to 11 years (median 5·5), and the diagnostic white cell counts ranged from $0·3–16·3\times10^9$/l (median 4·2). All had 'non-T-cell' acute lymphoblastic leukaemia. At the end of April 1990 length of follow up ranged from 27 to 193 months (median 147).

In the group diagnosed after 1980 there were 55 children (30 boys and 25 girls). Forty four (24 boys and 20 girls) were consecutively enrolled in UKALL VIII (arms A and B) and 11 (six boys and five girls) were consecutively enrolled in UKALL XA. The ages at diagnosis ranged from 0·3–13 years (median 4) and the white cell counts at diagnosis ranged from 0·8–670×10⁹/l (median 9·0). The immunological disease types were distributed as follows: 65% were common acute lymphoblastic leukaemia, 16% were pre-B, 5% were null, 5% were T-cell acute lymphoblastic leukaemia, and 9% were unclassifiable. At the end of April 1990 the length of follow up ranged from 23 to 121 months (median 76). When this group was matched with the group diagnosed before 1980, 15 children who had T-cell acute lymphoblastic leukaemia or white cell counts of more than 20×10⁹/l at diagnosis were excluded to make the groups comparable.

PRESCRIBING OF 6-MERCAPTOPURINE

Group diagnosed before 1980

Before 1980 modifications of the dose of 6-mercaptopurine if myelosuppression occurred were left to the clinicians' discretion, with the aim of keeping the white cell count between 2 and 3×10⁹/l. Prescribing of 6-mercaptopurine under these relaxed guidelines was compared with prescribing under the stricter regimens after 1980. Children diagnosed before 1980 received considerably lower cumulative doses of 6-mercaptopurine (range 22 106 to 49 563 mg/m^2; median 31 103) than comparable patients treated after that date (range 22 820 to 50 777 mg/m^2; median 40 499) (fig 1). The median difference between the two groups was 7743 mg/m^2 (95% confidence interval (CI) 4141 to 10 964 mg/m^2, $p<0·0001$).

This increase in the amount of 6-mercaptopurine that was prescribed cannot be accounted for solely by differences between protocols before and after 1980. The percentage increase in the median prescribed dose after 1980 was 22%, but the average increase in the 'target' cumulative dose of 6-mercaptopurine specified in the protocols after 1980 was only 9%. The largest difference was in UKALL III 'ordinary modified' E in which the potential dose of 6-mercaptopurine was 34% less than the potential dose after 1980, but only three children in the group diagnosed before 1980 received chemotherapy according to this protocol.

When boys and girls were analysed separately the increase in the amount of 6-mercaptopurine prescribed after 1980 was more pronounced for boys than for girls. Before 1980 boys' doses ranged from 23 365 to 49 563 mg/m^2 (median 31 019) and after 1980 'standard risk' boys' doses ranged from 29 746 to 50 777 mg/m^2 (median 41 71[illegible]). The median difference was 9025 mg/m^2 (95% CI 4264 to 13 302, $p<0·004$). For girls doses prescribed before 1980 ranged from 22 106 to 39 843 mg/m^2 (median 31 187) and after 1980 ('standard risk') doses ranged from 22 106 to 47 175 mg/m^2 (median 37 560). The median difference was 6394 mg/m^2 (95% CI 540 to 11 419 mg/m^2, $p<0·04$). Among those diagnosed before 1980 there was no significant difference in the amount of 6-mercaptopurine prescribed to boys compared with girls.

Group diagnosed after 1980

In the group diagnosed after 1980 ('all risk') the median cumulative dose of 6-mercaptopurine for boys was 42 099 mg/m^2 (range 29 746–50 777) whereas for girls it was 38 151 mg/m^2 (range 22 820–47 175) (fig 2). The median difference between the prescribed dose for boys compared with that for girls was 3647 mg/m^2 (95% CI 222 to 7468 mg/m^2, $p<0·03$).

The greater tolerance to 6-mercaptopurine shown by boys after 1980 was also reflected in the duration of the longest uninterrupted period they spent at the target dose of 75 mg/m^2. Their median time was 19 weeks (range 5–82) whereas for girls it was 13 weeks (range 2–45) ($p<0·05$) (fig 3). Girls also had more reductions in doses because of myelosuppression that were specified in the protocols (range 5–23, median 14·0) than boys (range 2–20, median 10·5) ($p<0·03$).

Non-compliance could potentially have affected these results, but children in this study group were also having red blood cell 6-thioguanine nucleotides (an active metabolite of 6-mercaptopurine) measured regularly as part

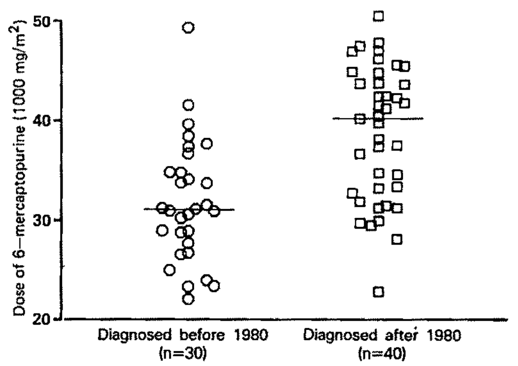

Figure 1 Cumulative dose of 6-mercaptopurine (mg/m^2) in study groups before (n=30) and after (n=40) 1980. Horizontal lines indicate median values (before 1980, 31 103 mg/m^2, after 1980, 40 499 mg/m^2).

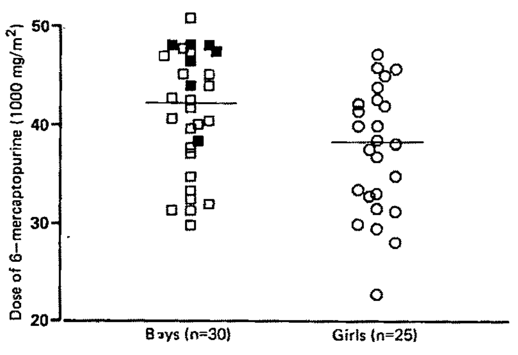

Figure 2 Cumulative dose of 6-mercaptopurine (mg/m^2) in boys (n=30) and girls (n=25) diagnosed after 1980. Horizontal lines indicate median values (boys 42 099 mg/m^2, girls 38 151 mg/m^2). Closed symbols indicate patients who subsequently relapsed.

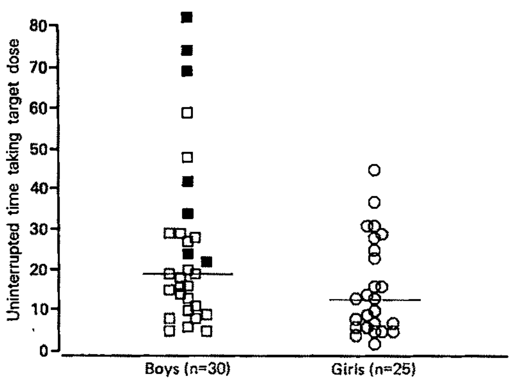

Figure 3 Longest uninterrupted time (weeks) spent at target dose of 75 mg/m² for boys (n=30) and girls (n=25). Horizontal lines indicate median times (boys 19 weeks, girls 13 weeks). Closed symbols indicate patients who subsequently relapsed.

of another study and non-compliance was not detected by this technique.

OUTCOME OF TREATMENT

Outcome of treatment among the children studied reflected national trends in the United Kingdom. At the time of analysis there had been nine relapses (two girls and seven boys in the group diagnosed before 1980 compared with four in the group diagnosed after 1980 ('standard risk') who were all boys. Log rank analysis indicated that there was an 18% improvement after 1980 in those still in first remission at five years ($\chi^2=3{\cdot}9$, $p<0{\cdot}05$; 95% CI 0·08 to 36·76%).

In the 'all risk' group diagnosed after 1980, outcome of treatment was also examined in relation to the amount of 6-mercaptopurine that had been given. There were seven relapses in the whole group (all boys). There was an estimated 15% increase in numbers remaining in remission at five years for those who received less than the group median cumulative dose of 6-mercaptopurine (one relapse) compared with those receiving more than the group median dose (six relapses) ($\chi^2=3{\cdot}69$, $p<0{\cdot}07$; 95% CI −3·6 to 33·2%) (fig 4). Five of the seven relapses occurred in the upper quartile for 6-mercaptopurine dosage.

There were no differences between the groups above and below the median dose of 6-mercaptopurine in diagnostic white cell count or type of leukaemia. There was an apparent excess of boys in the group above the median (18 boys and nine girls) and particularly in the upper quartile (11 boys and three girls) but this was not significant.

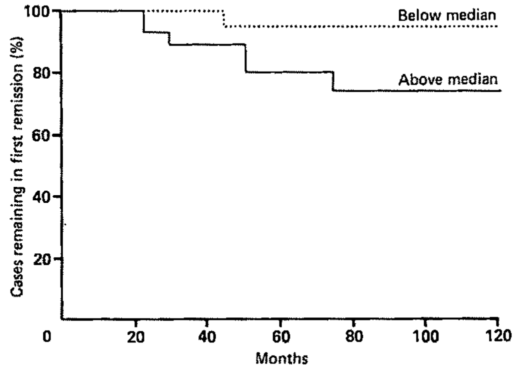

Figure 4 Percentage of cases remaining in first remission for those receiving above the group median dose of 40 011 mg/m² 6-mercaptopurine (n=27) and those receiving below the median dose (n=28); $\chi^2=3{\cdot}69$, $p<0{\cdot}07$.

Discussion

This single centre study with homogeneity of prescribing practice both before and after 1980 provides objective data to support the suggestion made by the Medical Research Council Working Party that more rigid prescribing criteria for drugs used in 'maintenance' treatment have contributed to the improved outlook for children with acute lymphoblastic leukaemia diagnosed after 1980.[1] In our patients the amount of 6-mercaptopurine that was prescribed undoubtedly increased after 1980, and much more than could be explained by changes in target doses specified in protocols. This was associated with a significant improvement in relapse free survival.

Because of the parallel adjustment of doses of 6-mercaptopurine and methotrexate during 'maintenance' chemotherapy it also follows that cumulative doses of methotrexate must have increased after 1980 as well. We believe that this is less likely to have had such a large effect on outcome, as the doses of methotrexate that are used are small.

Other studies have also shown an association between the amounts of 6-mercaptopurine and methotrexate prescribed during 'maintenance' chemotherapy and subsequent relapse of leukaemia.[6–8] In studies in which children were not treated with doses large enough to cause toxicity,[6 7] either because of the dose given in the protocol,[6] or because physicians did not comply,[7] the children who received less treatment did worse. In contrast, Silberman *et al* found that a small group of children with acute lymphoblastic leukaemia who received less than half their potential dose of 6-mercaptopurine because of pronounced toxicity related to treatment did better than similar patients who had less toxic reactions.

Our group diagnosed after 1980 show the same paradoxical phenomenon. Within this group most children were being treated with doses large enough to cause toxicity and were occasionally experiencing myelosuppression. Those who had more toxic reactions, and who were therefore being prescribed less 6-mercaptopurine seemed less likely to relapse, whereas those who tolerated uninterrupted target doses were more likely to relapse. This observation was not significant, but taken in the context of other studies points to a suggestive trend.

As more children are being prescribed as much 6-mercaptopurine as they can tolerate, individual differences in metabolism of the drug are becoming apparent. In the group diagnosed after 1980 the cumulative dose of 6-mercaptopurine that was tolerated by different patients ranged from 43% to 97% of the potential dose using the same prescribing guidelines. This almost certainly reflects underlying differences in the metabolism of 6-mercaptopurine among patients.[9]

As well as differences among patients the group diagnosed after 1980 also showed a significant difference in the tolerance of 6-mercaptopurine between the sexes, the boys being prescribed more 6-mercaptopurine and spending longer uninterrupted periods at the target dose specified in the protocol than girls using the same prescribing guidelines. This has been noted before over shorter times and presumably reflects a sex difference in the metabolism of 6-mercaptopurine.[2] This difference in tolerance between the sexes was not noted in the group diagnosed before 1980. The reason may be that with the earlier 'gentle' approach to treatment, doses of 6-mercaptopurine were not influenced as much by tolerance in either sex. In our study group boys had a worse outcome of treatment than girls, and it was striking that the boys most tolerant of 6-mercaptopurine subsequently relapsed more often.

The worse prognosis for boys with acute lymphoblastic leukaemia remains unexplained but perhaps sex differences in the metabolism of 6-mercaptopurine may in large part be responsible.[10] It may not be a coincidence that hypoxanthine-guanine phosphoribosyltransferase (the main enzyme responsible for converting the inactive native drug to its cytotoxic metabolites) is sex linked, and we are currently exploring this possibility.

In the meantime the findings of this single centre study clearly indicate that one of the chief differences between treatment protocols before and after 1980 is the amount of 6-mercaptopurine that was prescribed during 'maintenance' treatment as a result of changed criteria for reducing doses rather than a difference in recommended maximum doses in the protocols. Improvement in outlook for children in the United Kingdom with acute lymphoblastic leukaemia may in large part be because of this. The future intention to titrate the dose of 6-mercaptopurine to myelotoxicity in all children may prevent children who are more tolerant of the drug being inadvertently undertreated. It may, by the same mechanism, eliminate the difference in prognosis between the sexes.

This work was supported by the Leukaemia Research Fund.

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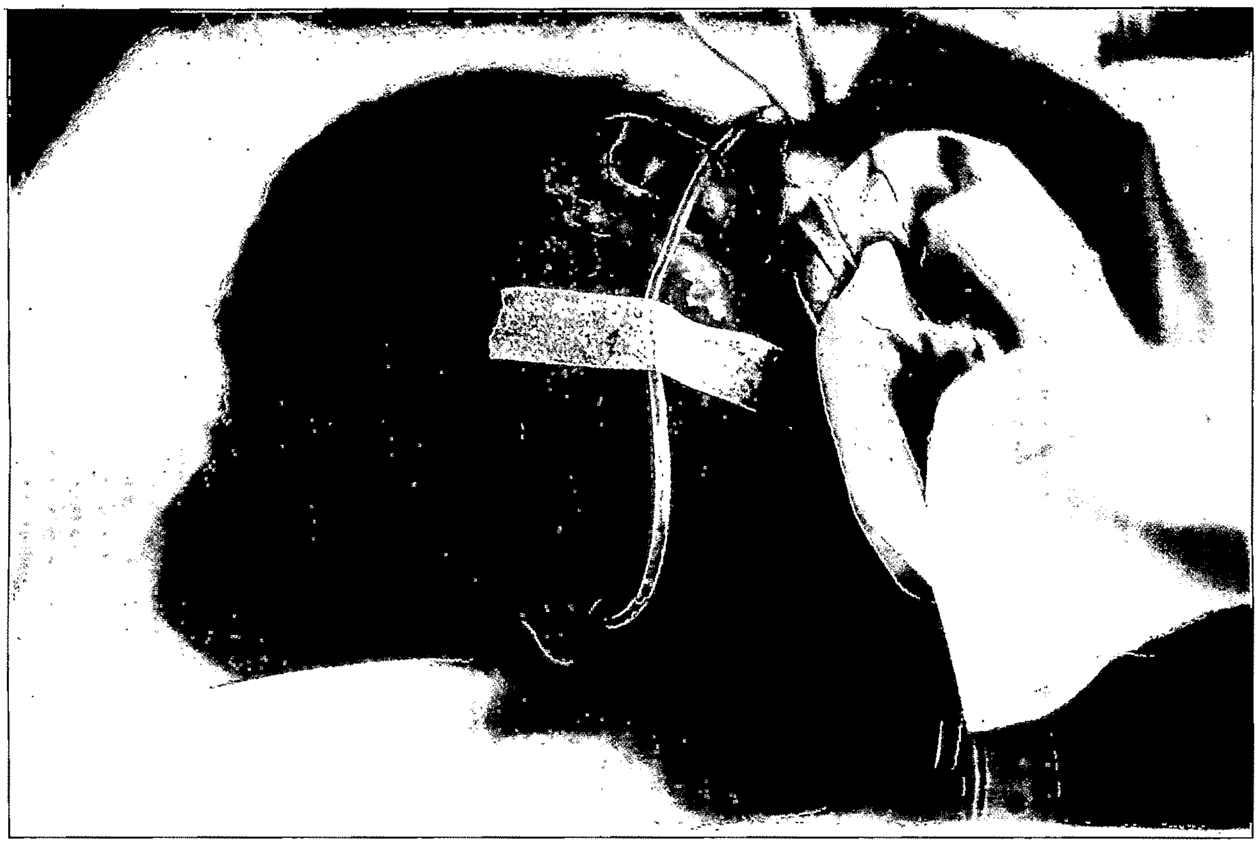

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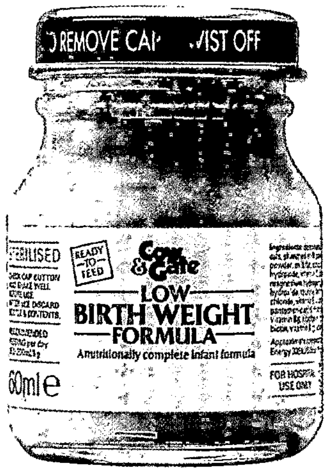

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Respiratory compliance in premature babies treated with artificial surfactant (ALEC)

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Abstract

In a randomised trial of artificial surfactant (ALEC) given at birth to 294 babies less than 34 weeks' gestation, the respiratory compliance was measured at 1, 6, 24, 48, and 168 hours after birth. In babies less than 29 weeks' gestation ALEC significantly improved the mean (SEM) compliance at 6 hours from 0·54 (0·06) to 0·91 (0·13) ml/cm H_2O/kg and at 24 hours from 0·57 (0·04) to 0·92 (0·10) ml/cm H_2O/kg. The improvements at 1, 48, and 168 hours were not significant. In babies of over 29 weeks' gestation the compliance was lower in the ALEC treated babies. This was significant only at one hour: 0·52 (0·03) compared with 0·71 (0·07) ml/cm H_2O/kg and only occurred in babies who were not ventilated.

Several randomised trials have shown that surfactant treatment of premature babies improves their oxygenation and ventilation. Only one has reported the effect of surfactant treatment on pulmonary mechanics in non-randomised babies.[1]

This paper reports measurements of the respiratory compliance made during a randomised trial of artificial surfactant given at birth to babies under 35 weeks' gestation. The surfactant, called artificial lung expanding compound (ALEC, Pumactant, Britannia Pharmaceuticals) is a protein free mixture of two pure phospholipids. The formulation, properties, and details of the trials have been described.[2–4]

Experiments to assess the effect of ALEC on respiratory compliance in premature rabbits at 27 days' gestation showed that it significantly improved the compliance after one hour's ventilation from 0·07 to 0·27 ml/cm H_2O/kg ($p<0·05$) and after one hour's spontaneous breathing from 0·10 to 0·58 ml/cm H_2O/kg.[5]

When ALEC was given prophylactically to babies less than 30 weeks' gestation, it significantly reduced the inspired oxygen concentration and ventilator pressure requirements in the first few days. It also significantly reduced the time babies required artificial ventilation, the time they were treated with more than 30% oxygen, the mortality, and the incidence of intracerebral haemorrhage.[2 4 6]

Accurately measuring respiratory compliance in ill premature babies is difficult.[7] In a clinical trial where babies are studied at predetermined times it is not possible to control for many of the factors that influence respiratory compliance. The techniques used for measuring compliance in this study were applied to babies in both treated and control groups. Thus despite the problems with possible inaccuracy of individual measurements the statistical comparison of two large randomised groups should be valid.

Subjects and methods

TRIAL PROTOCOL

Unselected babies born in Cambridge between 23 and 34 weeks' gestation were entered into the trial and randomised from sealed envelopes just before delivery. Babies randomised to surfactant were treated with 50–100 mg of ALEC powder, mixed with 1 ml of saline at 4°C just before use, and controls received 1 ml of saline. At birth surfactant or saline was put into the pharynx. If the baby was intubated, further doses were given through the endotracheal tube at 10 minutes, 1 hour, and 24 hours. Randomisation and giving the designated treatment were undertaken by the research team and these were not disclosed to the clinical teams. Babies were excluded from the analysis if they were stillborn or had gross congenital malformations. The trial was analysed by treatment as randomised.[8] The protocol was approved by the Cambridge District Health Authority ethics committee.

Two hundred and ninety four babies were entered into the trial, of whom 13 (4%) were excluded. Table 1 shows the distribution of factors in the two groups, in which compliance was measured, which might influence the severity of lung disease and thus respiratory compliance.

MEASUREMENT OF RESPIRATORY COMPLIANCE

Compliance was measured, where possible, at 1, 6, 24, 48, and 168 hours. Babies were supine in their own incubator. Sleep state could not be recorded. Signals were recorded on a polygraph (Gould 2600) with a full scale frequency response of 60 Hz. The pressure transducers (Mercury) and their tubing had a 90% rise time of approximately 30 ms, confirmed by the balloon burst technique. They were calibrated daily against a water column.

Tidal gas flow was measured using a pneumotachograph (Mercury F10L) with a dead space of 1·8 ml, this was attached either to a close fitting face mask or between the endotracheal tube and the ventilator circuit. It was calibrated with a syringe. The response was linear up to 18 l/minute. The flow signal was electronically integrated (Gould integrator No 13-4615-70) to tidal volume.

Oesophageal pressure was measured using hand made latex balloons approximately 2 cm

Table 1 Basic data for the two treatment groups

	All babies		*Babies <30 weeks' gestation*	
	Surfactant treated (n=102)	*Controls (n=108)*	*Surfactant treated (n=48)*	*Controls (n=48)*
Mean (SE) birth weight (g)	1441 (48)	1391 (44)	1089 (46)	1034 (38)
Mean (SE) gestational age (weeks)	29·6 (0·2)	29·7 (0·2)	27·4 (0·2)	27·4 (0·2)
No (%) males	24 (46)	55 (50)	24 (51)	29 (59)
No (%) PROM*	28 (27)	25 (23)	13 (28)	12 (24)
No (%) with pre-eclampsia	25 (25)	37 (34)	11 (23)	15 (31)
No (%) having caesarean section	57 (56)	62 (57)	23 (49)	29 (59)
No (%) going into labour	71 (70)	61 (56)	37 (79)	31 (63)
No (%) receiving antenatal:				
Steroids	7 (7)	7 (6)	5 (11)	4 (8)
β stimulants	28 (27)	25 (23)	19 (40)	16 (33)

*PROM, membrane ruptured for more than two days before delivery.

long, 0·5 cm wide, and 0·05 mm thick, on a size 6 French gauge neonatal feeding tube attached to a pressure transducer; a size 8 tube was considered to be too large for such small babies. The balloon was passed into the stomach and withdrawn into the oesophagus approximately 1 cm above the point where the baby's inspiration produced a negative deflection.[9] [10] Ventilator pressure was measured from the nasotracheal tube (usually 3·0 mm) near the pneumotachograph.

The randomised treatment was given by the team who measured the compliance. This possible source of bias was overcome by coding the recordings and analysing them blind at a later date.

Respiratory compliance was related to birth weight but not to length because it is difficult to measure in small sick babies.

Compliance was calculated from the recordings of 10 breaths without artifacts.

Dynamic compliance

Dynamic compliance was calculated for those babies who were breathing spontaneously. In intubated babies tidal volume and oesophageal pressure were measured during a brief disconnection from the ventilator. The pressure difference for this calculation was taken from the airway pressure at points of zero air flow. Expiratory volumes were used for calculations of tidal volume to minimise any error from leakage around the uncuffed endotracheal tube. In nonintubated babies the pneumotachograph was attached to a closely fitting face mask and recordings of tidal volume and oesophageal pressure were made when the baby was quiet and the face mask leak free (the inspiratory and expiratory volumes were equal).

Static compliance

Static compliance measurements were only made when babies were apnoeic or paralysed with pancuronium. The respiratory compliance was calculated from the tidal volume and the applied ventilator pressure difference measured accurately from a recording of the waveform. Tidal volume was measured when the inflating pressure had been held for at least 0·5 seconds and the volume exchange had reached a plateau.

Reproducibility of compliance measurements

The reproducibility of both static and dynamic compliance was tested in 20 infants whose clinical condition remained stable over several hours (assessed by lack of change in blood gas values and ventilator settings). Compliance measurements were made at 0, 30, 60, 120, 180, and 360 minutes. The intrasubject coefficient of variation was 22·3% for static compliance and 30·3% for dynamic compliance. The apparent variability of the measurement may be explained by the relatively long period over which measurements were made. More frequent measurements in such fragile babies would have been inappropriate.

MISSING DATA

Of 1405 occasions when compliance should have been measured satisfactory recordings were obtained on 777. Measurements were not possible on the other occasions for a number of reasons: the equipment was faulty or being serviced (n=353), the research staff were unavailable (n=52), the baby had died (n=31), or had been transferred out of the unit (n=67). In addition, from baby 140 onwards no six hour measurements were made because of logistic difficulties with trying to make three recordings in 24 hours.

The number of compliance measurements for each treatment group are shown in table 2 as a

Table 2 Number of measurements made at each time and the percentage of the babies alive and eligible for the measurement

Time after birth (hours)	*Surfactant treated*		*Controls*	
	No eligible to be measured	*No (%) measured*	*No eligible to be measured*	*No (%) measured*
All babies:				
1	102	98 (96)	108	104 (96)
6	54	49 (91)	52	46 (84)
24	99	85 (86)	106	93 (88)
48	98	77 (79)	105	90 (86)
168	96	72 (75)	103	63 (61)
Babies less than 30 weeks' gestation:				
1	48	46 (96)	48	46 (96)
6	23	22 (96)	20	20 (100)
24	46	43 (93)	46	43 (93)
48	45	38 (84)	45	44 (98)
168	43	36 (84)	43	36 (84)

The number of babies eligible for each compliance measurement is the number of live babies in the study at each time, taking account of the times when measurements were not possible (see text). No six hour measurements were done after baby 139.

Table 3 Number (%) of babies who were ventilated in each group at each time

Time after birth (hours)	*Surfactant treated*	*Controls*
All babies:		
1	54/98 (55)	57/104 (55)
6	21/49 (43)	24/46 (52)
24	35/85 (41)	45/93 (48)
48	28/77 (36)	41/90 (45)
168	15/72 (21)	16/63 (25)
Babies less than 30 weeks' gestation:		
1	32/46 (70)	43/46 (93)
6	13/21 (62)	17/20 (85)
24	26/43 (60)	34/43 (79)
48	23/38 (61)	31/44 (70)
168	12/36 (33)	18/36 (50)

percentage of the babies who were alive and eligible for measurements at each time. Table 3 shows the number of ventilated babies measured at each time and their percentage of the recordings made. The proportions in the two groups are not significantly different.

Results

Table 4 shows the compliance for each group at each time. The results are divided into two groups: babies between 23 and 29 weeks' gestation and babies between 30 and 34 weeks' gestation. This division was made because most respiratory problems occur in babies under 30 weeks' gestation and the results were then comparable with most other trials of surfactant treatment who only entered babies under 30 weeks' gestation.[11–14] Student's *t* test was used to investigate statistically significant differences.

BABIES OF 23 TO 29 WEEKS' GESTATION

The profile of change in compliance was different in the ALEC treated and control groups. The compliance of the controls increased gradually over the first seven days, whereas the compliance of the surfactant treated babies rose rapidly in the first six hours and remained at a similar level for the next seven days with no significant change. The compliance was significantly greater in the surfactant treated babies at six and 24 hours.

BABIES OF 30 TO 34 WEEKS' GESTATION

The compliance increased in both groups over the first seven days. It was lower in the ALEC treated babies than in the controls. This was only significantly different at one hour. This difference was confined to the babies who were not ventilated (0·57 (0·05) compared with 0·82 (0·08)) whereas in the ventilated babies there was no difference (0·44 (0·04) compared with 0·40 (0·03)).

Discussion

Accurately measuring respiratory compliance in ill premature babies is difficult. In intubated babies air may leak around the endotracheal tube reducing the measured tidal volume. Spontaneous respiratory efforts during mechanical ventilation alter the inflation volume, rendering some static compliance measurements inaccurate.[15] In babies who are paralysed to assist ventilation static compliance measurements can easily be made but the chest wall component, although small, is altered by the loss of tone in the muscles. In intubated babies the resistance to gas flow in the endotracheal tube will alter the apparent respiratory compliance. The magnitude of this varies with each baby and is related to the internal diameter and length of the endotracheal tube. The end occlusion technique[16] is often invalidated in babies with respiratory distress syndrome because they actively expire during the obstruction.[15]

Spontaneously breathing babies with lung disease have retraction of the chest wall during inspiration[17]; this reduces the tidal volume for an inspiratory force. The magnitude of the retraction depends on the gestation, the severity of lung disease, the strength of the diaphragmatic contraction, the baby's position and sleep state. If dynamic compliance is measured during disconnection from the ventilator lung volume may fall because the larynx is bypassed by the endotracheal tube.

The validity of the dynamic compliance measurements also depends on accurately recording oesophageal pressure. Unfortunately, this measurement may be inaccurate because the oesophageal pressure in very premature babies varies from the cardiac sphincter to the thoracic inlet and accurate, consistent placement of the oesophageal balloon is difficult.[7] Traditional methods of assessing the accuracy of oesophageal pressure measurements are not possible or useful in ventilated infants.[9] Leaks around the endotracheal tube can prevent complete airway occlusion and where occlusion is possible it is

Table 4 Compliance measurements (ml/cm H_2O/kg) for each group at each time

Time after birth (hours)	*Surfactant treated*		*Controls*		*p Value*
	No of babies	*Mean (SEM)*	*No of babies*	*Mean (SEM)*	
Babies 23 to 29 weeks' gestation:					
1	46	0·60 (0·06)	46	0·53 (0·05)	NS
6	22	0·91 (0·13)	20	0·54 (0·06)	<0·05
24	43	0·92 (0·10)	43	0·57 (0·04)	<0·01
48	38	0·75 (0·09)	44	0·65 (0·08)	NS
168	36	1·03 (0·09)	36	0·89 (0·10)	NS
Babies 30 to 34 weeks' gestation:					
1	52	0·52 (0·03)	59	0·71 (0·07)	<0·05
6	29	0·56 (0·05)	28	0·72 (0·09)	NS
24	43	0·71 (0·07)	50	0·78 (0·07)	NS
48	41	0·73 (0·07)	47	0·88 (0·10)	NS
168	34	0·91 (0·08)	28	1·16 (0·11)	NS

very difficult to get the ratio of oesophageal and airway pressure close to unity because of the pressure gradient within the oesophagus.[7 17] We have previously reported a good correlation in ventilated babies between pressure changes measured by the oesophageal balloon and those measured directly from a catheter draining a pneumothorax.[10] Although this confirms the ability of the oesophageal balloon to reflect intrathoracic pressure changes, it does not ensure that oesophageal pressure will reflect pleural pressure changes in sick premature babies without a pneumothorax. Throughout the study care was taken to position the balloon similarly in each infant. Consequently the measurement at least gave a method of comparison between infants.

Static compliance was measured only in apnoeic ventilated babies and dynamic compliance in spontaneously breathing babies, thus we cannot compare the two measurements. It has been suggested that static compliance may be higher than dynamic compliance measured at the same time.[18] Any effect this might have on our results is reduced by having a similar number of each measurement in the two randomised groups.

Despite possible difficulties with respiratory compliance measurements, our results are comparable with those found by others in premature infants of similar weight.[19 20] Thus despite relatively high coefficients of variation, this suggests our techniques were as accurate as those used by others. In physiological studies designed to measure respiratory compliance it is possible to control for many of the factors that affect compliance. This is rarely possible in clinical studies. This paper reports comparisons between two randomised groups of ill premature babies who were well matched, apart from surfactant treatment, for the factors that might influence respiratory compliance. As described it was not always possible to measure the respiratory compliance because of equipment failure, neonatal deaths, discharges, or technical difficulties. However, these data losses affected both ALEC treated and control babies to a similar extent. It is therefore valid to compare the overall results from the two groups.

It is possible that saline instilled into the trachea may have altered the respiratory compliance.[21] Any effect of instilling saline would not affect the comparison between the two groups, however, because ALEC was suspended in exactly the same volume of saline as was given to the control babies. Both groups therefore received identical volumes of saline. This volume was used because it was the volume that was considered to be safe for routine endotracheal suction.

This study has shown that artificial surfactant (ALEC) given at birth to babies between 23 and 29 weeks' gestation improves respiratory compliance during the first hours of life so that by 6 hours of age, the ALEC treated babies had a respiratory compliance 69% greater than that of the controls, an effect which persisted at 24 hours. After this the difference in compliance was reduced. This apparent loss of differential effect may be due to three factors. Firstly, more control babies died during this time (13 controls compared with 10 treated with ALEC) thereby removing more babies with the worst compliance from the control group. Secondly, the compliance in the controls improved slowly during the first few days to reach the level which was achieved in the surfactant treated babies at about six hours. Thirdly, after a few hours the surfactant may have been inhibited by protein exudation on to the alveolar surface[22] or the beneficial effect of ALEC reduced by some other process such as degradation or absorption. If the latter explanation is true, it may be that further doses of surfactant might be beneficial. Interestingly, these changes in compliance are similar to the time course for change in compliance shown in ventilated premature lambs treated with another synthetic surfactant.[23] The effect of ALEC on compliance has a similar time course to the improvements in oxygenation and ventilator pressures which were significantly improved by 12 hours after birth.[4]

Milner *et al* measured compliance at resuscitation in a group of intubated babies after they had received one dose of ALEC, and before and immediately after they were given a second dose, and showed no apparent effect.[24] The results of their measurements are not at variance with this study and again suggest that ALEC takes a few hours to produce its maximum effect after administration at birth.

ALEC had no beneficial effect on the compliance of babies of 30–34 weeks' gestation. The compliance was significantly lower at the one hour measurement in the surfactant treated babies. Many babies in this gestational age group were not very ill. A minority were ventilated and most of those were ventilated for less than one day. Thirty percent did not receive any oxygen, and of those that did receive oxygen 70% had it for less than 72 hours. Exploring the data showed that this effect was present only in babies who were not ventilated. This difference was not seen in the babies less than 30 weeks possibly because most were intubated and ventilated from birth. A possible interpretation of this finding is that surfactant should only be given to those babies who require intubation and ventilation at birth. It is possible that positive pressure ventilation distributes the surfactant to the periphery of the lung whereas in spontaneously breathing babies substantial amounts may remain in the large airways and increase their resistance.

In a non-randomised study Davis *et al* measured respiratory mechanics after administration of calf surfactant extract to premature babies with established respiratory distress syndrome.[1] In 10 ventilated babies, despite improvement in gas exchange, no significant improvement in pulmonary mechanics could be demonstrated. In 25 infants who were only receiving continuous positive airways pressure there was an improvement in compliance.

The artificial surfactant ALEC given at birth to babies under 30 weeks' gestation improves the compliance of the respiratory system by 6 hours of age. This improvement in lung function reflects the lower incidence of respiratory distress syndrome, lower oxygen and ventilatory requirements, and reduced mortality seen in babies treated with this artificial surfactant. This simple, protein free surfactant should be a useful addition to the therapeutic weapons of the neonatologist in babies of this age.

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Favouritism and child abuse

Social and cultural differences between nations may make it unsafe to generalise from data derived from one country. Nevertheless a paper from Japan (Tanimura *et al*, *Lancet* 1990; **336**:1298–9) provides food for thought about child abuse and there seems to be no a priori reason why the findings shoud not be generally applicable.

One in 10 abused children in a national survey were from multiple births, 15 times the expected rate. In 80% of cases where a twin was abused the other twin was not. The factors leading to abuse for both twins or of only one were different. Abuse of both twins was associated with social, economic, and marital problems and personality disorder in the parents. When one twin was abused that twin was likely to be chronically ill or to have been separated from the parents for a long time, though parental problems were still common. The parents often admitted a strong preference for the other child.

The findings suggest that a potent combination leading to child abuse is parental stress together with some 'unlovable' feature in the child leading to favouritism. Health professionals must be alert to this and the even more important possibility that appropriate intervention might redress the balance and prevent abuse, in singletons as well as in twins.

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Lung function abnormalities at 6 months of age after neonatal intensive care

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Abstract

Respiratory function was studied in 46 preterm infants (median gestational age 28 weeks) at 6 months of age. Respiratory function was assessed by measurement of thoracic gas volume, airways resistance (from which specific conductance was calculated), and functional residual capacity. To determine the effect of the duration of neonatal intermittent positive pressure ventilation (IPPV) on respiratory function, the infants' results were divided into three groups: group A, no IPPV; group B, IPPV for less than seven days; and group C, IPPV for more than seven days. Measurements of thoracic gas volume and functional residual capacity were similar to published reference ranges and there were no significant differences between the three groups. Measurements of airways resistance and specific conductance were higher than published reference ranges (mean airways resistance of group A, 34 cm H_2O/l/sec; B, 34·1 cm H_2O/l/sec, and C, 30·4 cm H_2O/l/sec) but there was no significant difference between the three groups. The 95% confidence intervals of the difference of the means between groups A and B were −6·94 to 6·73 cm H_2O/l/sec and between groups A and C −3·8 to 11·0 cm H_2O/l/sec. Our results suggest that factors other than neonatal ventilation may be more important in the pathogenesis of chronic lung function abnormalities in preterm infants.

Chronic lung damage is a frequent complication of preterm delivery.[1 2] Such infants have a high mortality and morbidity, with an increased rehospitalisation rate and risk of respiratory infection.[3] Many infants wheeze at follow up,[3–5] and lung function abnormalites may be demonstrated during the first year of life.[6 7]

Several studies have suggested that positive pressure support is particularly important in the pathogenesis of chronic lung disease.[8] Before 1969 bronchopulmonary dysplasia, the most severe form of chronic lung disease, was rarely seen, although spontaneously breathing infants were often exposed to 100% oxygen. After 1969, however, bronchopulmonary dysplasia was seen and this coincided with the introduction of continuous positive airways pressure.[9] Bronchopulmonary dysplasia was also described in ventilated infants who had required an oxygen concentration of less than 60%.[10] The level of peak airway pressure used during mechanical ventilation seemed to be an important determinant of lung damage. Taghizadeh and Reynolds in 1976 reported a highly significant association between the most serious changes of bronchopulmonary dysplasia and use of peak inspiratory pressures in excess of 35 cm H_2O.[11] Moreover, the incidence of bronchopulmonary dysplasia was reduced by limiting the peak inspiratory pressure to 35 cm H_2O; this change occurred despite inspired oxygen concentrations during ventilation that were often above 80%. Stocks and Godfrey further incriminated positive pressure support by demonstrating lung function abnormalities at follow up among infants who had received artificial ventilation, but not among those who had been treated with other forms of respiratory support.[12]

The studies implicating positive pressure support in the pathogenesis of chronic lung damage were performed over a decade ago. At that time slow ventilator rates with long inspiratory times were employed during mechanical ventilation. High frequency positive pressure ventilation[13] and patient triggered ventilation[14 15] are now more frequently used; both modes of ventilation incorporate short inspiratory times and fast frequencies. A further advance in neonatal ventilation over the 10 year period has been in improvements in the ventilators themselves.[16] Changes in the ventilators and modes of neonatal ventilation may have reduced the damaging effect of positive pressure support.

In this study we have tested the hypothesis that, in 1990, neonatal ventilation is less important in the pathogenesis of chronic lung damage. As an index of chronic lung damage we have measured lung function at 6 months of age. To assess the effect of neonatal ventilation we have compared the lung function results of infants who required no neonatal ventilation with those who were ventilated and also between two groups of preterm infants who required different durations of neonatal ventilation. If our hypothesis is correct then we should expect similar lung function results between infants with and without neonatal ventilation and between infants ventilated for different durations.

Patients and methods

PATIENTS

Forty six preterm low birthweight infants were enrolled into the study and reviewed at 6 months of age (range 23–25 weeks). The infants had a median (range) birth weight of 1210 (506–1900) g and median (range) gestational age of 28 (23–34) weeks. All the infants who had respiratory problems had suffered from respiratory distress syndrome. All but four of the infants had required some form of respiratory support either an increase in the inspired oxygen concentration or mechanical ventilation. Infants requiring mechanical ventilation had been ventilated at rates of between 60 and 120 breaths per minute and had an inspiratory to expiratory (I:E) ratio of 1:1·2. Mechanical ventilation was started in the labour suite if the infant made inadequate respiratory efforts or during the course of the infant's illness if either a respiratory acidosis developed (pH <7·25) or the infant had frequent minor or a major apnoea. Infants with severe bronchopulmonary dysplasia who were still oxygen dependent at 6 months of age were excluded from the study.

Methods

The infants were seen in the paediatric respiratory laboratory at 6 months of age. Their medical history was taken, height and weight measured, and the child examined. Lung mechanics, thoracic gas volume, airways resistance, and functional residual capacity were then measured after sedation. Specific conductance was calculated from thoracic gas volume and airways resistance. The infant was sedated with oral chloral hydrate (100 mg/kg) and lung mechanics measured during quiet sleep in the supine position.

Thoracic gas volume and airways resistance were measured using a whole body plethysmograph. The infant breathed through a face mask, which was connected to the rebreathing bag via a heated pneumotachograph and was sealed around the infant's nose and mouth using silicone putty to ensure an airtight seal. The infant breathed through a heated, humidified rebreathing system to avoid box pressure changes due to the heating and cooling of respired gas. Thoracic gas volume was measured at the end of a normal inspiration and airways resistance at two thirds of maximum inspiratory flow by the classical techniques of Dubois *et al* suitably modified for infants.[17] [18] Thoracic gas volume was calculated from five breaths during occlusion and at least five separate occlusions were made. Airways resistance was calculated from at least 10 breaths. All measurements (thoracic gas volume and airways resistance) were corrected for the apparatus dead space (15 ml) and resistance (8 cm H_2O/l/sec, measured at flows of between 5 and 15 l/minute). Traces were analysed blind to clinical details.

After completion of the measurements of the thoracic gas volume and airways resistance the infant's face mask was connected to a spirometer (Gould Pulmonet III) for the measurement of functional residual capacity. The spirometer has an internal carbon dioxide absorber and an adjustable oxygen supply and has a total volume of six litres. The water sealed spirometer incorporates a digital display of functional residual capacity, which was recorded on the trace at 15 second intervals. Equilibration was assumed to have occurred when there had been no change in the functional residual capacity readout over a 30 second period; all the traces were coded and then analysed blind to clinical details. From the trace the equilibration point and expiratory level were determined and functional residual capacity calculated. The results were then converted to body temperature, pressure, and saturation (BTPS) conditions.

The reproducibility of the measurement of thoracic gas volume and airways resistance was determined in 16 children of similar gestational and postnatal age to the study population. Calculation of thoracic gas volume and airways resistance was as described above.

The coefficient of variation calculated from measurements of thoracic gas volume and airways resistance performed before and after infants had been removed and returned to the body plethysmograph was 6% for thoracic gas volume and 9% for airways resistance. To assess the reproducibility of the measurement of functional residual capacity, two separate measurements were made in 20 children of similar gestational and postnatal age to the study population. The coefficient of variation of these measurements was calculated as 7·3%.

STATISTICAL ANALYSIS

To assess the effect of ventilation and the duration of mechanical ventilation (IPPV) on lung function the infants were divided into three groups: no IPPV (group A), IPPV less than seven days (group B), and IPPV greater than seven days (group C). The clinical characteristics of the three groups are shown in table 1. Lung function was then compared between the three groups and differences assessed for significance using the Wilcoxon rank sum test. The confidence intervals were calculated with the appropriate p value from the standard error of the difference between the means of groups A and B and groups A and C.

TRIAL SIZE

We had demonstrated the mean (SD) resistance of a previous group of 20 consecutive preterm infants studied at 6 months of age to be 35 (7·5) cm H_2O/l/sec. Using these results, 12 patients would be required in each group to detect a difference in resistance of 10 cm H_2O/l/sec between groups with 85% power at the 5% level.

Ethical permission for this study was granted by the King's College Hospital ethics committee.

Results

No significant difference in functional residual capacity, thoracic gas volume, specific conductance, or airways resistance was demonstrated

Table 1 Clinical characteristics of the three groups of infants divided according to the duration of ventilation. Results are median (range)

	Birth weight (g)	*Gestational age (weeks)*
Group A (n=12)	1386 (1100–1800)	29·5 (27–32)
Group B (n=22)	1190 (516–1900)	29 (25–34)
Group C (n=12)	980 (506–1512)	27 (23–32)

Table 2 Lung function data related to the duration of neonatal ventilation. Results are means and mean differences with 95% confidence intervals

	Airways resistance (cm $H_2O/l/sec$)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance ($sec^{-1}/cm\ H_2O$)
Group A	34·00	28·82	40·69	0·135
Group B	34·07	27·62	36·23	0·148
Group C	30·43	33·95	37·32	0·167
B–A	+0·07 (−7·35 to +7·49)	−1·20 (−5·73 to +3·33)	−4·46 (−10·55 to +1·62)	+0·013 (−0·031 to +0·056)
C–A	−3·57 (−11·48 to +4·35)	+5·13 (−0·29 to +10·55)	−3·38 (−8·99 to +2·24)	+0·032 (−0·020 to +0·083)

Table 3 Results of infants not ventilated in the neonatal period (group A)

Case No	Birth weight (g)	Gestational age (weeks)	Oxygen duration in neonatal period	Weight at time of measurement (kg)	Airways resistance (cm $H_2O/l/sec$)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance ($sec^{-1}/cm\ H_2O$)
1	1312	28	0	5·60	22·0	25·5	34·	0·237
2	1440	28	10 hours	5·40	32·0	24·4	53·	0·108
3	1426	29	0	6·48	39·0	32·[illegible]	40·[illegible]	0·099
4	1346	28	1 hour	6·35	39·0	24·[illegible]	33·[illegible]	0·121
5	1270	30	0	6·42	43·0	41·4	45·[illegible]	0·080
6	1780	32	4 hours	7·28	19·0	30·0	33·[illegible]	0·219
7	1800	31	2·5 days	6·80	28·0	*	29·[illegible]	0·177
8	1640	31	1 day	6·00	42·0	*	42·[illegible]	0·107
9	1320	31	1·5 days	6·85	43·0	27·0	34·[illegible]	0·099
10	1100	28	5 days	4·20	24·0	35·0	50·[illegible]	0·198
11	1210	27	0	6·60	33·0	21·[illegible]	51·[illegible]	0·089
12	1500	30	0·5 day	6·15	44·0	26·[illegible]	40·[illegible]	0·091

*Results are not available.
No infant was admitted to hospital during the first six months.

Table 4 Results of infants ventilated for less than seven days (group B)

Case No	Birth weight (g)	Gestational age (weeks)	Oxygen duration after IPPV (days)	Ventilation (days)	No of admissions to hospital (first six months)	Weight at time of measurement (kg)	Airways resistance (cm $H_2O/l/sec$)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance ($sec^{-1}/cm\ H_2O$)
13	1900	34	2	5	1 (viral infection)	5·44	42·0	25·5	49·0	0·060
14	1170	29	6	5	—	6·25	49·0	26·0	46·7	0·060
15	1200	28	1	2	—	5·60	50·5	27·3	45·0	0·079
16	1210	28	0·5	1	—	7·30	25·0	24·2	29·9	0·183
17	1180	27	1	3	1 (bronchiolitis)	7·00	23·0	26·0	30·7	0·202
18	876	27	2	5	—	7·50	28·0	26·0	33·6	0·142
19	1274	32	1	4	—	7·05	27·0	25·1	32·4	0·163
20	816	25	0·4	4	—	7·55	23·0	30·6	40·0	0·144
21	1730	32	1·5	3	—	7·03	25·0	28·3	53·0	0·108
22	1778	29	0·1	1·3	—	6·90	40·0	28·0	28·7	0·126
23	516	29	0·1	2	1 (chest infection)	4·99	33·0	37·5	46·9	0·129
24	840	26	1	2	—	4·10	22·0	28·9	39·0	0·284
25	1554	29	0	2	—	6·95	52·0	23·7	25·0	0·111
26	1018	28	2	6	—	6·60	52·0	28·0	28·3	0·104
27	996	29	1·5	2·5	—	5·44	25·0	23·5	25·5	0·288
28	1300	33	2	0·5	—	5·10	45·0	38·5	42·9	0·101
29	1430	31	0·1	0·5	—	6·00	27·1	18·3	34·3	0·202
30	1070	28	0·2	0·5	—	7·46	31·0	20·0	31·5	0·137
31	1279	30	1·5	0·3	—	6·90	31·0	41·0	45·6	0·102
32	720	27	1·5	0·9	—	5·58	28·0	31·5	32·2	0·198
33	1138	27	0·8	0·8	—	5·10	46·0	27·4	27·8	0·153
34	1300	29	0	0·3	—	7·60	25·0	30·4	29·3	0·179

Table 5 Results of infants ventilated for more than seven days (group C)

Case No	Birth weight (g)	Gestational age (weeks)	Oxygen duration after IPPV (days)	Ventilation (days)	No of admissions to hospital (first six months)	Weight at time of measurement (kg)	Airways resistance (cm $H_2O/l/sec$)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance ($sec^{-1}/cm\ H_2O$)
35	810	26	6	11	1 (chest infection)	3·80	28·0	37·0	44·5	0·121
36*	886	26	36	42	—	5·40	21·0	34·[illegible]	37·6	0·160
37	685	24	6	14	1 (chest infection)	4·73	36·0	34·0	36·6	0·113
38	1074	28	4	11	1 (chest infection)	5·10	23·0	25·[illegible]	41·2	0·153
39	1120	27	2	8	—	6·30	26·0	36·0	35·8	0·170
40	1468	32	2	8	—	6·17	30·0	39·[illegible]	39·2	0·138
41*	506	23	6	28	1 (chest infection)	3·75	24·0	27·0	41·0	0·271
42*	1444	27	11	20	—	6·27	19·2	22·[illegible]	25·3	0·328
43*	1512	29	5	23	—	6·12	27·0	40·[illegible]	40·0	0·160
44	1092	30	5	8·5	—	3·94	45·0	41	39·1	0·144
45	682	24	2	10	1 (febrile convulsion)	6·20	35·0	32·[illegible]	35·1	0·130
46	836	29	3	9	1 (bronchiolitis)	5·25	51·0	33·[illegible]	32·4	0·115

*Oxygen dependent for 28 days or more.

between the three groups of infants regardless of the duration of neonatal ventilation (tables 2, 3, 4, and 5). The 95% confidence intervals of the difference of the means of groups A (34 cm H_2O/l/sec) and B (34·1 cm H_2O/l/sec) are −6·49 to 6·73 cm H_2O/l/sec and between groups A (34 cm H_2O/l/sec) and C (30·4 cm H_2O/l/sec) are −3·8 to 11·0 cm H_2O/l/sec.

Discussion

We report lung function measurements of infants of 6 months of age, rather than those of school age or older, as we thought it important to audit current ventilation practices. Our results could therefore be used, if important abnormalities were demonstrated, to influence that current practice. We investigated very preterm infants and compared our results with those in earlier reports. Our study audits a complete cohort of such preterm infants excluding only those with bronchopulmonary dysplasia who were oxygen dependent at 6 months of age. Our study population were ventilated using modern ventilators by high frequency positive pressure ventilation (IPPV). In this cohort we have been able to report a number of indices of lung function, thoracic gas volume, airways resistance, and functional residual capacity.

Airways resistance measurements in the 46 infants included in the present study showed a slightly greater interindividual variability (SD 9·5 cm H_2O/l/sec) than we had demonstrated in a previous group of 20 consecutive preterm of infants, whose data we used to calculate the trial size. As the increase in variability was only small our trial size remained appropriate. Enrolling 12 patients in each group still gave us 75% power at the 5% level to detect a difference in resistance of 10 cm H_2O/l/sec between groups and 85% power at the 5% level to detect a difference of 12 cm H_2O/l/sec.

In the present study we have not included a control group as it was felt unjustifiable to sedate healthy 6 month old infants to perform plethysmographic measurements to establish a normal range. Indeed, one may also query if such infants' results would be appropriate to use as a reference range for comparison with the results of a very preterm population. Many published reference ranges relate only to term infants or a mixture of preterm and term infants.[19] As a consequence functional residual capacity, measured by dilution methods, is reported to vary from 21·5 ml/kg to 37 ml/kg.[19] The mean data of the present study fall within this wide range. For each measurement there was a wide scatter of results. This may reflect differences in our patients regarding their gestation at birth and severity of their respiratory illness.

We have not demonstrated a significant difference in functional residual capacity, thoracic gas volume, or airways resistance in infants ventilated for different lengths of time nor between ventilated and non-ventilated infants. Our measurements of thoracic gas volume are very similar to those of Stocks and Godfrey[12] and previously published reference ranges.[20 21] Our airways resistance results in all three groups of infants were similar to Stocks and Godfrey's ventilated infants but higher than their non-ventilated infants and the published reference range.[20] Our technique of measurement and its reproducibility was very similar to that used previously,[12] and the number of patients we enrolled was twice that included in the earlier study.[12] We therefore think that we are reporting a true difference in the findings of the two studies. The high airways resistance of all our three groups and the failure to demonstrate a difference in airways resistance between the groups, regardless of the need for neonatal ventilation, may be explained by the immaturity of the patients we examined.[12] Two other recent reports have failed to confirm an association between neonatal ventilation and lung function abnormalities.[22 23] Both groups reported that poor airway function at school age was independent of neonatal respiratory illness and closely associated with low birth weight.[22 23] Further evidence to support this association was our finding of abnormal airways resistance in a group of four infants who, although requiring no form of respiratory support in the neonatal period, had been born very preterm between 27 and 30 weeks of gestational age.

Plethysomography cannot be performed on oxygen dependent infants thus, in this study, infants with severe bronchopulmonary dysplasia had to be excluded. Our results cannot therefore represent a complete audit of neonatal ventilation. All five infants with severe bronchopulmonary dysplasia excluded from our study were born before 26 weeks completed gestation and had many complications such as patent ductus arteriosus, infection, and pulmonary air leak. Until a much larger group of these infants can be collected and studied it will not be possible to determine the contribution of a single factor such as neonatal ventilation in the pathogenesis of severe chronic lung damage. All other infants, however, consecutively cared for on our unit, were included in this study. The similarity of results from our non-ventilated and ventilated infants and lack of difference in airways resistance regardless of the duration of ventilation suggests that factors other than neonatal ventilation may be more important in the pathogenesis of chronic lung function abnormalities.

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Hyperactivity

Article number 3861d of the Archivist Transatlantic Guide runs as follows: 'doctors who say "tom-ay-toe" frequently diagnose hyperactivity whilst those who say "tom-ar-toe" rarely do'. This basic rule of medical conduct has never, to my mind, been explained very convincingly on the basis of attitudinal and psychosocial differences between the two nations. Most British paediatricians take in such facts as that 6% of all children in Baltimore County are given stimulant drugs for hyperactivity[1] with more than a touch of incredulity, not to say apprehension. Pathogenesis, too, tends to be viewed differently, more emphasis being given to biological factors in America and to psychosocial determinants in Britain.

Recent work at the National Institutes of Health in Bethesda (Zametkin *et al*, *New England Journal of Medicine*, 1990; **323**:1361–6) will have revived interest in biological mechanisms. Using positron emission tomography cerebral glucose metabolism was studied in 50 normal adults and in 25 adults who had been diagnosed as hyperactive in childhood, still had symptoms, and had hyperactive children. A significant reduction in overall cerebral glucose metabolism was found in the hyperactive subjects and the reduction was greatest in the premotor cortex and the superior prefrontal cortex, areas of the brain known to be concerned with control of attention and motor activity.

A symptom such as hyperactivity is bound to be multifactorial in its origins. People who are still hyperactive as adults and who also have hyperactive children are obviously a select group, but the demonstration of changed cerebral glucose metabolism is of great interest. It is not known whether these changes are primary or secondary or whether they occur in children as well as in adults. Neither is it known whether drug treatment would reverse the changes. Clearly there is much to elucidate but it seems a promising path to follow.

ARCHIVIST

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Day case ligation of patent ductus arteriosus in preterm infants: a 10 year review

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Abstract

Since 1978, 136 preterm babies received ligation of a patent ductus arteriosus as day cases. A total of 122 babies whose notes were available for review, with a median gestational age of 27 weeks (range 23–35) and median birth weight of 960 g (range 470–2750), were transported distances of up to 80 miles. The median ages at ligation with and without previous medical management with indomethacin were 23 and 15 days, respectively. One hundred and ten (90%) babies were dependent on ventilatory support, but extubation was achieved at a median time of 10 days after ligation, regardless of postnatal age at the time of ligation. There were no deaths associated with the operation, and no complications resulting from transportation. The hospital mortality was 15 (12·3%), and the most important (and significant) adverse factor was a preoperative fractional inspiratory oxygen content greater than 0·3. The results of this study show that day case ligation of the patent ductus arteriosus is safe, and if it is carried out early will reduce the time before extubation and discharge from the intensive care unit.

The ductus arteriosus persists in 20%–30% of infants who are born weighing less than 2000 g, and causes appreciable morbidity in many.[1–3] The resultant respiratory failure may require prolonged ventilatory support, and is associated with increased mortality. The morbidity can, however, be reduced by early closure of the duct.[4]

Indomethacin is usually the first line of treatment; if this fails ligation of the duct may be considered, but the practical details vary considerably among individual neonatal units. Ducts may be ligated in the incubator in the neonatal unit, or in an operating theatre of the same hospital.[5 6] This, however, requires that a cardiothoracic surgeon has to travel what may be a long distance to and from the neonatal unit, which is not a cost effective use of his time. There has been a single report of neonates undergoing duct ligation as a day case.[7]

It has been our practice to have each baby transported from the referring neonatal unit to this supraregional cardiothoracic centre for duct ligation. The infants were then transported back to their units immediately after the procedure. In this study we report our 10 year experience of day case duct ligation, with reference to the related medical management.

Patients and methods

Between November 1978 and May 1989, 136 preterm infants with isolated patent ductus arteriosus were admitted for ligation, 119 as day cases; 122 patient records were available and have been reviewed. The median gestational age was 27 weeks (range 23–35) and the median birth weight 960 g (range 470–2750, 116 of whom weighed less than 1500 g). Three regional neonatal units referred three quarters of the patients. A number of district general neonatal units collectively referred the remainder. Two of the regional neonatal units are in Leeds, and one is in Sheffield (35 miles away). The district hospitals were scattered throughout Yorkshire and North Trent.

The patent ductus arteriosus was diagnosed and treated in accordance with the medical protocol preferred locally. If these measures failed, ligation was requested. Before ligation the diagnosis was confirmed by a paediatric cardiologist using cross sectional cardiac ultrasonography. Particular care was taken to ensure that it was an isolated problem, and that it was of a size that was likely to be haemodynamically and clinically important.

Ligation of the duct was usually arranged at a day's notice. The responsibilities of the referring medical team were sending one unit of cross matched blood, obtaining parental consent, and providing an experienced nurse and medical escort for the infant. On arrival at this hospital, which was timed to coincide with a space in the routine operating list, the infant was transferred to the operating theatre.

A posterolateral thoracotomy was made through the fourth intercostal space, and the duct ligated with a single 2/0 Persalls suture. The procedure required careful retraction with minimal compression of the lung, to provide good visibility of the operative field while maintaining ventilation of both lungs; we find the Killingbeck paediatric lung retrator indispensible.[8] Chest drainage was not used routinely, but the lungs were fully inflated before the chest cavity was closed.

Demographic statistics and details of medical management before and after operation were recorded, as were the complications, and details of progress after ligation.

The data were not normally distributed, and so non-parametric tests (Mann-Whitney U, Spearman rank correlation, and χ^2 tests) were used for analysis. A probability of <0·05 was accepted as significant.

Results

The various subgroups were comparable (table

Table 1 Clinical details of infants treated by duct ligation after medical treatment. Figures expressed as median (range) except where otherwise stated

Treatment group	*No of infants*	*Gestation (weeks)*	*Birth weight (g)*	*Age at diagnosis (days)*	*Age at ligation (days) after medical treatment*			
					Without indomethacin		*With indomethacin*	
					No of infants	*Median (range)*	*No of infants*	*Median (range)*
Regional neonatal unit A	30	28 (24–34)	1020 (620–2750)	5	25	16 (5–63)	5	13 (3–17)
Regional neonatal unit B	32	27 (23–33)	1000 (470–2330)	5	16	13·5 (6–25)	16	22·5 (10–42)
Regional neonatal unit C	31	27 (23–35)	940 (550–1550)	6	21	21 (7–44)	10	23 (16–36)
District general hospitals (D)	29	26 (23–34)	920 (680–2340)	7	7	15 (5–39)	22	26 (9–48)
Total	122	27 (23–35)	960 (470–2750)	6	69	15 (5–63)	53	23 (3–48)

1). The median ages at the time of clinical diagnosis of the patient ductus were also similar (roughly 6 days). Of the 122 infants reviewed, 53 had received indomethacin before referral for duct ligation (table 1). Ducts were ligated significantly earlier in patients who did not receive indomethacin ($p<0{\cdot}001$).

All hospitals practised some degree of fluid restriction before ligation, but it was possible to withdraw restrictions within five days of operation (table 2). Mechanical ventilation was required by 110 infants (90%) with a median fractional inspired oxygen concentration (F_IO_2) of 0·3 before ligation (table 3). Infants of less than 26 weeks' gestation (43%) or weighing less than 1000 g at birth (51%) were ventilated longer (median 15 and 14 days, respectively) than the older and larger infants (median 8 and 6 days) after ligation ($p<0{\cdot}01$). The F_IO_2 given on the day after ligation was temporarily higher, and was not related to gestational age or birth weight.

Table 2 Policies of fluid restriction practised in infants with patent ductus arteriosus. Values are expressed as median (interquartile range)

Treatment group	*Amount of fluid given (ml/kg/day)*	
	Before ligation	*After ligation*
Regional neonatal unit A	135 (120–150)	150 (150–165)
Regional neonatal unit B	120 (100–130)*	162 (150–175)
Regional neonatal unit C	135 (120–150)	175 (155–175)
District general hospitals (D)	150 (120–150)	150 (150–175)
Those treated with indomethacin	130 (120–150)	160 (150–175)
Those not treated with indomethacin	120 (105–150)	165 (150–175)
Total	130 (120–150)	162 (150–175)

*$p<0{\cdot}05$ compared with groups A, C, and D. None of the other differences are significant.

After ligation, the median intervals to withdrawal to continuous positive airway pressure (CPAP) and extubation were 7 and 10 days, respectively. Postnatal age at ligation (in those aged 13 days or more) did not influence this (figure). Those in whom the duct was ligated between 9 and 12 days of age, however, had longer median intervals to withdrawal of CPAP (13·5 days, interquartile range (IQR) 7–23), and extubation (20·5 days, IQR 9–25) than those in whom the duct was ligated between 17 and 20 days (6·5, IQR 4–10·5, and 11·5, IQR 5·5–17·5), and those in whom it was ligated when they were more than 25 days of age (7, IQR 2·75–11·75, and 10, IQR 3–15), respectively ($p<0{\cdot}05$). Of the three groups in which there were infants older than 17 days, a larger proportion received indomethacin ($p<0{\cdot}05$) but there was no difference in the amount of preoperative oxygen supplementation.

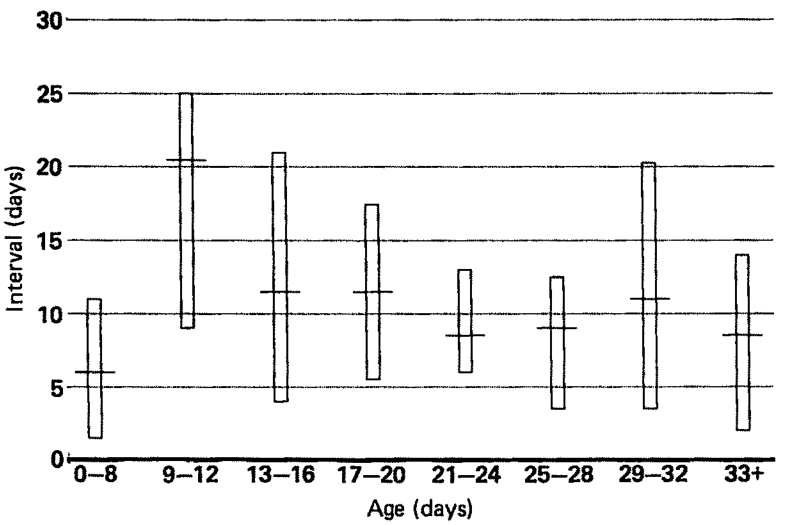
No deaths were directly related to the operation, though 15 of the 122 babies (12%) subsequently died of problems associated with prematurity (table 4). Of 63 infants who required preligation F_IO_2 concentrations of over 0·3, 13 died ($p<0{\cdot}05$).

Two babies had haemorrhages that required re-exploration, but no damage to major vessels was discovered (table 5), and one of these died five days later of rapidly progressive respiratory failure. One infant had a phrenic nerve palsy of uncertain aetiology; segmental lobar collapse affecting particularly the right upper lobe was a serious problem on day 1. Of the 50 infants who had had cranial ultrasound examinations before

Table 3 Degrees of ventilatory support provided, and intervals between ligation withdrawal of CPAP, and extubation. Values are expressed as median (interquartile range)

Treatment group	*Inspiratory oxygen concentration (%)*		*Intervals (days) from ligation to:*	
	Before ligation	*After ligation*	*Withdrawal to CPAP*	*Extubation*
Regional neonatal unit A	35 (30–40)	50 (39–63)	7·5 (4–14)	13·5 (6–23)
Regional neonatal unit B	25 (23–30)*	30 (25–40)**	6 (2–9)***	8·5 (3–13)†
Regional neonatal unit C	30 (25–40)	50 (31–60)	8 (3–14)	10 (4–15)
District general hospitals (D)	50 (30–58)	68 (40–80)	10 (4–18)	14 (5–20)
Those treated with indomethacin	35 (30–60)	43 (30–70)	8 (4–17)	10 (5–20)
Those not treated with indomethacin	30 (25–40)	45 (30–60)	7 (3–14)	11 (4–20)
Total	30 (25–43)	45 (30–65)	7 (4–15)	10 (5–20)

*$p=0{\cdot}001$ compared with groups A and D; **$p=0{\cdot}001$ compared with groups A, C, and D; ***$p=0{\cdot}05$ compared with group D; and †$p=0{\cdot}05$ compared with group A.



Interval from day of ligation to extubation. The bars indicate the median and interquartile range.

Table 4 Late hospital deaths

Cause	*No of infants*
Respiratory failure	10
Necrotising enterocolitis	3
Renal failure	1
Septicaemia	1
Total	15/122 (12%)

Table 5 Complications of duct ligation

Complication	*No of infants*
Haemorrhage	2
Stridor	2
Lobar collapse:	
Right	21
Left	6
Pneumothorax:	
Right	1
Left	6
Total	37/122 (30%)

and after ligation only two showed progression, both from normal to grade 1 intraventricular haemorrhage.

No problems were reported concerning the transportation.

Discussion

This study has shown that day case ligation of the patent ductus arteriosus in preterm infants is safe. There was no mortality associated with the operation or the transport, and morbidity was low. Comparison of the hospital mortality with previous reports (10–40%, most above 20%) indicates that our overall management policy was satisfactory.[1 9 10]

There were no problems reported concerning transportation despite infants weighing as little as 470 (and more recently 430 g) being transfered from hospitals as far as 80 miles away. The smooth transportation of these infants was facilitated by the excellent network of motorways and A roads linking this city with its neighbours.

The results suggest that neonatal unit B, in which fluid restriction was most rigidly practised, achieved the most favourable ventilatory statistics. Though this is in keeping with previous research, we cannot state categorically that this was the sole reason, as many other variables must be taken into account.[13 14]

Those infants who underwent duct ligation between the ages of 9 and 12 days were the slowest to be weaned from ventilatory support; we are uncertain of the reason for this. Among the older infants more had received indomethacin than among the younger, but there were no differences in demographic or ventilatory measurements.

The observed lobar collapse predisposes to a temporary but manageable deterioration in ventilation after ligation. This, however, is not a problem peculiar to preterm infants, and may be seen in patients of all ages after major thoracic and abdominal operations. More intriguing however, is the tendency to collapse of the right upper lobe. The upper lobe bronchus, which is the most dependent major airway in the supine position, may drain inadequately if ciliary function is upset after the anaesthetic, thereby allowing formation of mucous plugs and subsequent collapse.

Northway and Jacob *et al* have suggested that delay in achieving duct closure may be detrimental, causing progression to bronchopulmonary dysplasia.[11 12] Duct ligation did, however, control the cardiorespiratory failure with consequent benefits; mechanical ventilation was withdrawn, and the volume of fluid and thus energy was increased to more optimal amounts, so promoting better growth than was encountered preoperatively.

Indomethacin is least successful in closing the ducts of infants with very low birth weights and with severe respiratory distress syndrome requiring assisted ventilation.[15] Rudd *et al* showed that in a group of babies weighing less than 1500 g at birth the incidence of patent ductus arteriosus was 31%. Of these, 87% initially closed with indomethacin, but 47% reopened.[16] Many of the infants treated by day case ligation of the ductus were comparable with this group (116 (95%) weighed less than 1500 g at birth) and were thus likely to experience reopening of a ductus that had closed after medical treatment, and unlikely to benefit from a protracted trial of this treatment.

Cotton *et al* reported that extubation was achieved earlier, and after lower expenditure in patients who had undergone early duct ligation rather than awaiting the result of prolonged medical treatment.[17] Other authors have supported this view, reporting that the mortality associated with a haemodynamically important patent ductus had risen significantly since the introduction of indomethacin.[18] They found that results were more satisfactory when early ligation was routine.

Gersony *et al*, however, reported the results of a multicentre trial that did not confirm these findings.[19] A total of 421 infants were randomised to receive one of three treatment protocols. The first group received indomethacin together with restricted fluids and diuretics as the primary treatment. The second received indomethacin, and the third underwent duct ligation only after initial fluid restriction had failed to close the duct. The study showed no significant differences between the length of time that ventilatory support was required by each group, or in the incidence of complications such as bronchopulmonary dysplasia, intracranial haemorrhage, and necrotising enterocolitis. The mortality was also similar.

Conclusion

Because our patients are a highly selected group we are not in a position to compare medical and surgical treatment of patent ductus arteriosus. Our results do show conclusively, however, that surgical closure can be done safely even after transportation of the ventilated infant to a cardiothoracic centre with appropriate expertise. Where local circumstances are such that the regional cardiothoracic centre is remote from neonatal intensive care facilities, we believe that the policy of day case ligation of the ductus makes most economic use of the time of the surgeon while keeping responsibility for the ventilation and medical care of the infant in the hands of the referring paediatric team.

We suggest that if a preterm infant who is dependent on the ventilator has an arterial duct of sufficient size to merit medical treatment, then failure of this treatment should lead to immediate consideration of surgical ligation.

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Fibreoptic bronchoscopy without general anaesthetic

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Abstract

We have used flexible fibreoptic bronchoscopy using sedation and local anaesthesia in 50 children aged 2–19 years (median 10) using an Olympus BFP20 instrument. Indications were opportunistic pneumonias (n=11), persistent atelectasis (n=11), recurrent pneumonia (n=7), miscellaneous lower airway disease (n=7), recurrent wheezing (n=3), haemoptysis (3), to diagnose infection or rejection of heart-lung transplants (n=3), stridor (n=2), suspected airway compression (n=1), evaluation of tracheostomy (n=1), and suspected foreign body (n=1). In 43 cases (86%) the diagnosis was related to the primary indication. In five (10%) unrelated abnormalities were found, and five (10%) were normal. In 13 (26%) treatment was altered as a result of flexible fibreoptic bronchoscopy. Complications were transient respiratory arrest (n=2), hypoxia (n=2), pneumonia (n=2), and laryngospasm (n=1). All complications were followed by complete recovery.

Our results suggest that flexible fibreoptic bronchoscopy is safe. Advantages over rigid bronchoscopy include greater visual range, fewer complications, and the avoidance of a general anaesthetic. Though invasive it can yield important diagnostic and therapeutic information.

The introduction of the flexible fibreoptic bronchoscope in 1969 transformed the practice of adult chest medicine by extending the diagnostic and therapeutic capabilities of the physician. Paediatric bronchoscopy has usually been done with a rigid (open tube) bronchoscope under general anaesthesia, to either retrieve foreign bodies or diagnose anatomical abnormalities, and most authorities still assert that this is the best way to visualise the airways in children.[1] Technological advances have, however, led to the development of small flexible fibreoptic bronchoscopes that are suitable for use in infants and children without a general anaesthetic.

This paper gives our experience with fibreoptic bronchoscopy done under sedation with local anaesthetic in the diagnosis and treatment of paediatric pulmonary disorders.

Patients and methods

Between January 1987 and November 1989, 50 flexible fibreoptic bronchoscopies were carried out in children aged 2–19 years (median 10) (table 1). Those with opportunistic pneumonias were immunocompromised patients with acute lymphoblastic and myeloid leukaemia, and (in one case) AIDS related complex. The patients with persistent atelectasis had lobar collapse that had failed to respond to treatment with antibiotics given intravenously and physiotherapy. In seven of the cases the bronchoscopy was done to diagnose or exclude connective tissue diseases of the lung parenchyma such as fibrosing alveolitis. Six patients were bronchoscoped to see if there was an anatomical cause for recurrent pneumonia. The indication in three other patients was recurrent wheezing which had failed to respond to antiasthmatic drugs. In these cases another cause for the wheezing, such as bronchomalacia, was suspected. Three patients had bronchoscopies to determine the cause of unexplained haemoptysis—for example, a bronchial polyp. In three cases the bronchoscopy was done to help differentiate between infection and rejection in patients with cystic fibrosis who had had heart-lung transplants. In two patients chronic stridor, thought not to be caused by laryngomalacia, was the indication. In one patient airway compression caused by a vascular ring was the reason. In another, evaluation of a tracheostomy was the indication. The aim was to detect the presence of tracheomalacia or of any granulation tissue that may have required removal before decannulation. In a further patient there was a vague history of possible foreign body inhalation but no signs on examination or on the chest radiograph. The presence of a foreign body was thought unlikely and a flexible fibreoptic bronchoscopy was done to avoid the need for a general anaesthetic. In the last patient the bronchoscopy was done both to help investigate the cause of recurrent pneumonia and to do a bronchogram to diagnose the presence and extent of bronchiectasis. Some of the patients, in particular those who were severely immunocompromised with recurrent opportunistic pneumonia, required more than one flexible fibreoptic bronchoscopy.

Table 1 Indications for fibreoptic bronchoscopy

Clinical indication	*No (n=50)*
Opportunistic pneumonias	11
Persistent atelectasis	11
Miscellaneous lower airway disease	7
Recurrent pneumonia	6
Recurrent wheezing	3
Haemoptysis	3
To diagnose infection or rejection of heart-lung transplants	3
Stridor	2
Suspected airway compression	1
Evaluation of tracheostomy	1
Suspected foreign body	1
Bronchogram in patient with recurrent pneumonia	1

In no case did this result from technical failure of the initial bronchoscopy.

An Olympus BF P20 (external diameter 4·9 mm, working channel 2·2 mm) was used (figure). The bronchoscopy was carried out in a bronchoscopy suite with facilities for resuscitation. A nurse trained in the techniques of fibreoptic bronchoscopy assisted the operator. A second nurse or doctor observed the patient and the monitors. Patients were fasted for at least four hours before the procedure. Premedication was with pethidine 1–2 mg/kg and midazolam 0·1–0·3 mg/kg, both given intravenously. Lignocaine gel was used to anaesthetise the nose and 2% lignocaine liquid (instilled through the working channel of the bronchoscope) was used to anaesthetise the vocal cords, carina, and both main bronchi. Additional aliquots of 2% lignocaine liquid were sometimes instilled in the lower airway to control coughing. The bronchoscope was inserted through the nose. A small volume bronchial lavage with 5–10 ml of normal saline was done on each occasion. To avoid contamination from the upper respiratory tract suction was not used until the tip of the bronchoscope was beyond the carina, and the first aspirated sample was discarded.

Large volume bronchoalveolar lavage (30–120 ml depending on the size of the child) was done if there was any suspicion of interstitial lung disease. The bronchoscope was wedged in a segmental bronchus and normal saline injected through the working channel. All specimens were sent for cytological and microbiological analysis. Cytological analysis comprised a total cell count and percentage values of macrophages, neutrophils, lymphocytes, and eosinophils. Cells were also examined for evidence of fungal, viral, protozoal, and parasitic infection. Thirty five transbronchial biopsies were done, all under fluoroscopic control. For safety reasons only one lung was biopsied at any one bronchoscopy. All patients were continuously monitored with an oximeter. Oxygen was given through the free nostril or through the suction channel of the bronchoscope if low oxygen saturations were recorded on the oximeter. A chest radiograph was performed after all bronchoscopies. Naloxone was given routinely at the end of the procedure in the bronchoscopy suite to reverse the effects of the pethidine. Flumazenil was given to reverse the effects of the midazolam if indicated.

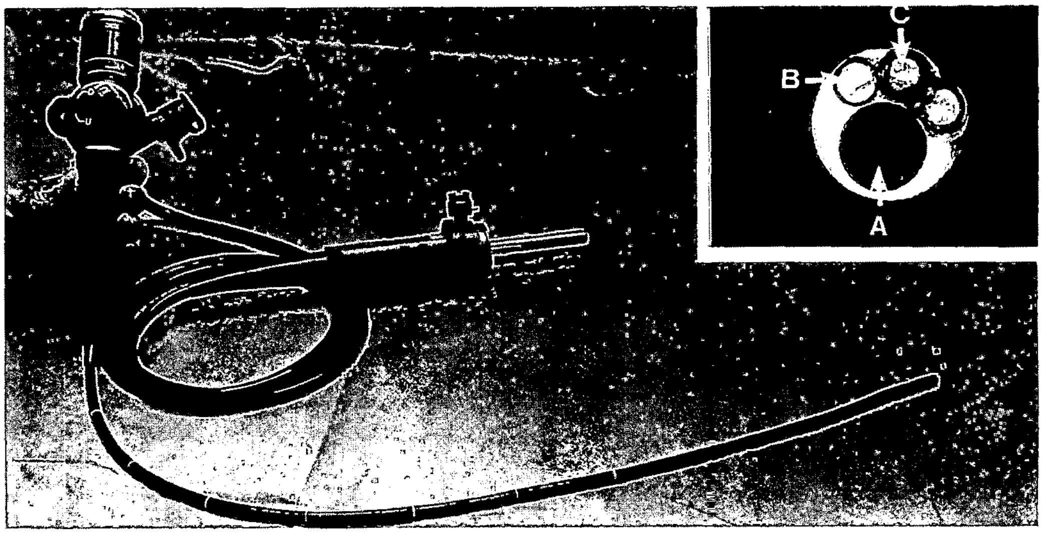
Results

The diagnoses are shown in table 2. In 43 cases (86%) the abnormal findings were directly related to the primary indication for flexible fibreoptic bronchoscopy. In five cases (10%) abnormalities unrelated to the primary indication were found. In another five the findings were normal. In some patients both abnormalities related to the primary indication and unrelated abnormalities were found.

Chronic inflammation was diagnosed if there was a chronic inflammatory infiltrate with a predominance of lymphocytes in the biopsy specimen. Acute inflammation was diagnosed when erythematous mucosa and purulent secretions were seen during bronchoscopy. The opportunistic organisms causing the pneumonias were *Pneumocystis carinii* (n=2), *Candida albicans* (n=2), cytomegalovirus (n=2), and measles (n=1). In none of the above cases was the organism identified on examination of the sputum. In those pneumonias in which an organism was identified this was done on analysis of the bronchoalveolar lavage fluid and confirmed in two cases by the biopsy specimen. None of our patients required open lung biopsy. Haemoptysis in our three cases was secondary to severe infection, a haemangioma, and idiopathic

Table 2 Diagnoses at fibreoptic bronchoscopy

Diagnosis	*No (n=50)*
Chronic inflammation/fibrosis	19
Generalised acute inflammation	8
Opportunistic infection with identified organism	7
Normal	5
Haemoptysis: cause found	3
Tracheal/bronchial compression	3
Bronchomalacia	2
Bronchial stenosis	1
Bronchial plugging	1
Cytotoxic lung damage	1



The Olympus BF P20 fibreoptic bronchoscope. Box: end view of tip of bronchoscope. A=working channel, B=fibreoptic light bundles, and C=lens.

pulmonary haemosiderosis, respectively. Tracheobronchial compression was secondary to lymph nodes in two cases and a vascular ring in a third. Bronchomalacia was attributed to the Williams-Campbell syndrome in one and confirmed by bronchography, which showed severe airway collapse on expiration.

Bronchial stenosis with persistent atelectasis was diagnosed in a patient with a history of a severe pneumonia who was immunologically normal, and bronchial plugging with persistent atelectasis was found in a patient with cystic fibrosis. Cytotoxic lung damage was diagnosed in a patient with leukaemia who had interstitial fibrosis and calcification in the alveolar walls on biopsy. In 13 (26%) of cases, treatment was changed as a direct result of flexible fibreoptic bronchoscopy. Six of the seven patients with opportunistic pneumonia in whom the responsible organism was identified were started on the appropriate treatment. In the seventh (with measles) treatment of the giant cell pneumonia was not changed as there is no specific treatment. One of the patients with cytomegalovirus pneumonia had a further bronchoscopy two weeks after treatment with gancyclovir to assess whether further treatment was necessary. Cytomegalovirus was still present in the lavage fluid and treatment was continued. One patient with *Streptococcus pneumoniae* in his lavage fluid, but not in his sputum, was started on the appropriate antibacterial treatment. Another patient who had been diagnosed as having left main bronchus stenosis was given prophylactic antibiotics and physiotherapy during the winter. A patient with a tracheostomy who had been considered suitable for decannulation did not have the procedure after the discovery of severe tracheal stenosis at the tracheostomy site. A patient with compression of the left main bronchus that was thought to be caused by a vascular ring (as a result of variation in size of the bronchial lumen with systole and diastole) was referred for cardiac catheterisation, which showed a pulmonary artery sling; this was cured by operation. The patient with bronchomalacia was referred for bronchial stenting.

Major complications comprised respiratory arrest (n=2), hypoxia (n=2), pneumonia (n=2), and transient laryngospasm not requiring intubation (n=1). Both cases of respiratory arrest occurred in patients with pulmonary hypertension and cor pulmonale. In both reversal was rapidly achieved with naloxone. In the hypoxic patients the oxygen saturation's lowest reading was 70% and lasted for only a few seconds. The pneumonias were mild and treated in both cases by antibiotics given orally; they did not prolong the patients' stay in hospital. In the patient with laryngospasm it had not previously been possible to examine the tracheobronchial tree adequately. This patient was subsequently referred to a thoracic surgeon for a rigid bronchoscopy. Minor complications were also encountered.

Two patients had hallucinations during the bronchoscopy, secondary to midazolam, and required further sedation with pethidine. Some of the patients who had had biopsies had slight blood streaking of the sputum for a few hours after the procedure. Several of the patients had minor epistaxis, which in all cases stopped before the end of the procedure, having responded to compression of the nares for a few minutes. All complications were transient and followed by complete recovery. There was total amnesia for the procedure in all cases.

Discussion

Flexible fibreoptic bronchoscopy is a routine procedure in adult chest medicine. Wood started his pioneering work into paediatric flexible fibreoptic bronchoscopy in 1978 in the United States.[2] He used the bronchoscope to diagnose and treat a wide variety of disorders including some that had previously required rigid bronchoscopy. He successfully carried out the bronchoscopies under sedation, thus avoiding the need for a general anaesthetic with all its attendant complications.

Flexible fibreoptic bronchoscopes are the instruments of choice in most bronchoscopies. They can be passed through the nose or mouth, though an endotracheal tube, or through a tracheostomy. They provide a dynamic view of both the upper and lower airways. Laryngomalacia, tracheomalacia, the effects of endobronchial lesions such as granulation tissue and tumours, or extrabronchial compression can safely be seen without the distortion caused by a rigid tube. The small directional tip of the flexible bronchoscope enables better visualisation of the upper lobe bronchi and distal bronchi. Flexible fibreoptic bronchoscopy can be done with the child in bed and does not require moving a sick patient with several intravascular lines to an operating theatre. Furthermore, the expense of using the operating and recovery rooms is avoided.

Rigid bronchoscopy requires a general anaesthetic and is associated with subglottal oedema that can lead to stridor and laryngospasm. The rigid instrument is, however, more suitable in certain circumstances. These include removal of foreign bodies, operative manipulations such as dilatation of a bronchial stenosis, and the evaluation of large haemoptyses during active bleeding. Rigid bronchoscopes are also more useful in the search for H-type tracheo-oesophageal fistulas and the critical evaluation of the posterior aspect of the larynx, as in a patient with bilateral vocal cord paralysis.[3]

Indications for flexible fibreoptic bronchoscopy in Wood's series of 1095 patients published in 1984 comprised stridor (24%), atelectasis (17%), miscellaneous lower airway disease (17%), tracheostomy evaluation (15%), miscellaneous upper airway disease (9%), recurrent or persistent pneumonias (7%), wheezing (6%), suspected airway compression (3%), and haemoptysis (2%).[2] Indications in our series were somewhat different. This is partly because our hospital is a tertiary referral centre and partly because there has been an increase in the number of patients undergoing immunosuppressive treatment in the treatment of malignancies and after transplantation. In one of our cases the indication for flexible fibreoptic bronchoscopy was a suspected foreign body. If the presence of a foreign body is strongly suspected we refer the patient for a rigid bronchoscopy. If the evidence is equivocal we perform a diagnostic flexible bronchoscopy and then refer the patient for a rigid bronchoscopy if a foreign body is found. Using this approach in a series of 52 patients Wood and Gauderer found foreign bodies in 10 (19%).[4] Rigid bronchoscopy was thus avoided in most patients.

There are no absolute contraindications to bronchoscopy but clearly patients with severe airway obstruction, pulmonary hypertension, severe coagulopathies, or profound hypoxaemia are at higher risk than others. Both our patients who had respiratory arrests had pulmonary hypertension. The arrests were thought to be caused by the premedication rather than effects of the procedure.

Diagnoses relevant to the indication for the bronchoscopy were found in most of our cases. In a series of 695 patients Wood found abnormalities relevant to the primary indication for bronchoscopy in 76% of cases, abnormalities not relevant to the primary indication in 15%, and normal findings in 9%.[5] Normal results were often important in excluding abnormalities. Surprisingly the diagnostic yield among the opportunistic pneumonias was greater on the results of culture of lavage fluid than on examination of the biopsy specimen. An accompanying neutrophilia in the lavage fluid was a helpful confirmatory sign of pyogenic infection. De Blic *et al* found that analysis of bronchoalveolar lavage in immunocompromised children with opportunistic pneumonias led to a specific diagnosis in 60% of cases.[6] Using the method described above contamination from upper airway secretions was avoided in most cases. In adults specimens may be collected with brushes protected within a catheter to avoid contamination.[7] Collection systems currently available are, however, too large to pass through the paediatric flexible bronchoscope. The diagnosis of the infectious agent in an opportunistic pneumonia may mean that open lung biopsy is not necessary. In Wood's series and in ours treatment was changed in an appreciable number of cases as a direct result of the bronchoscopy.

The flexible fibreoptic bronchoscopy can occupy a large part of the airway. This relative disadvantage in a patient with already compromised respiration can be overcome by using appropriately small instruments, and there are now ultrathin instruments with an outer diameter of 2·2 mm.

All the complications that we encountered were transient and followed by complete recovery. In retrospect, the dose of pethidine used in the two patients with cor pulmonale who developed respiratory failure was too high. The effects of pethidine and midazolam can rapidly be reversed by naloxone and flumazenil, respectively. In Wood's series of 1095 procedures there were four important complications, none of which was fatal. Two patients developed a pneumothorax, one had laryngospasm requiring brief intubation, and one developed a lung abscess after a bronchogram. Twenty eight patients developed minor complications including epistaxis, transient laryngospasm, transient bradycardia and anaesthetic complications, none of which required intervention.[2] One death after flexible fibreoptic bronchoscopy has been reported (in a 2 year old child with severe pulmonary hypertension, congestive heart failure, and a history of severe laryngomalacia).[8]

Rigid bronchoscopy is well established in paediatric practice. Flexible fibreoptic bronchoscopy is a safe procedure with low risks which has appreciable advantages over the rigid instrument and is useful for the evaluation of children with pulmonary disorders. We feel that the change in treatment in 26% of our cases as a direct result of the bronchoscopy is strong justification for its use.

Development of small fibreoptic bronchoscopes with extended capabilities is under way. Adaptors that attach to the endotracheal tube and allow a bronchoscope to be inserted while maintaining mechanical ventilation are available. Studies have begun using the working channel as a port for low frequency oscillatory ventilation, an improvement that will provide an extra margin of patient safety.[9] Wire nests that can be passed through the working channel of the flexible fibreoptic bronchoscopy are being developed for the retrieval of foreign bodies. Balloons to dilate strictures and fibreoptic laser for use in patients with conditions such as subglottic stenosis are also being developed.

Normal values exist for differential cell counts in bronchoalveolar lavage fluid in adults, and these are helpful in diagnosing various diseases such as cryptogenic fibrosing alveolitis. Knowledge of normal and abnormal paediatric cell counts in lavage fluid would be helpful in the diagnosis of interstitial lung diseases in children. A randomised controlled trial comparing the diagnostic yield in opportunistic pneumonias obtained by analysis of lavage fluid and bronchoscopic biopsy specimens compared with those obtained at open lung biopsy would be of great interest. The rarity of these conditions, however, would make the logistics of such a trial difficult.

We predict that the role of flexible fibreoptic bronchoscopy in paediatric pulmonology will expand in the future.

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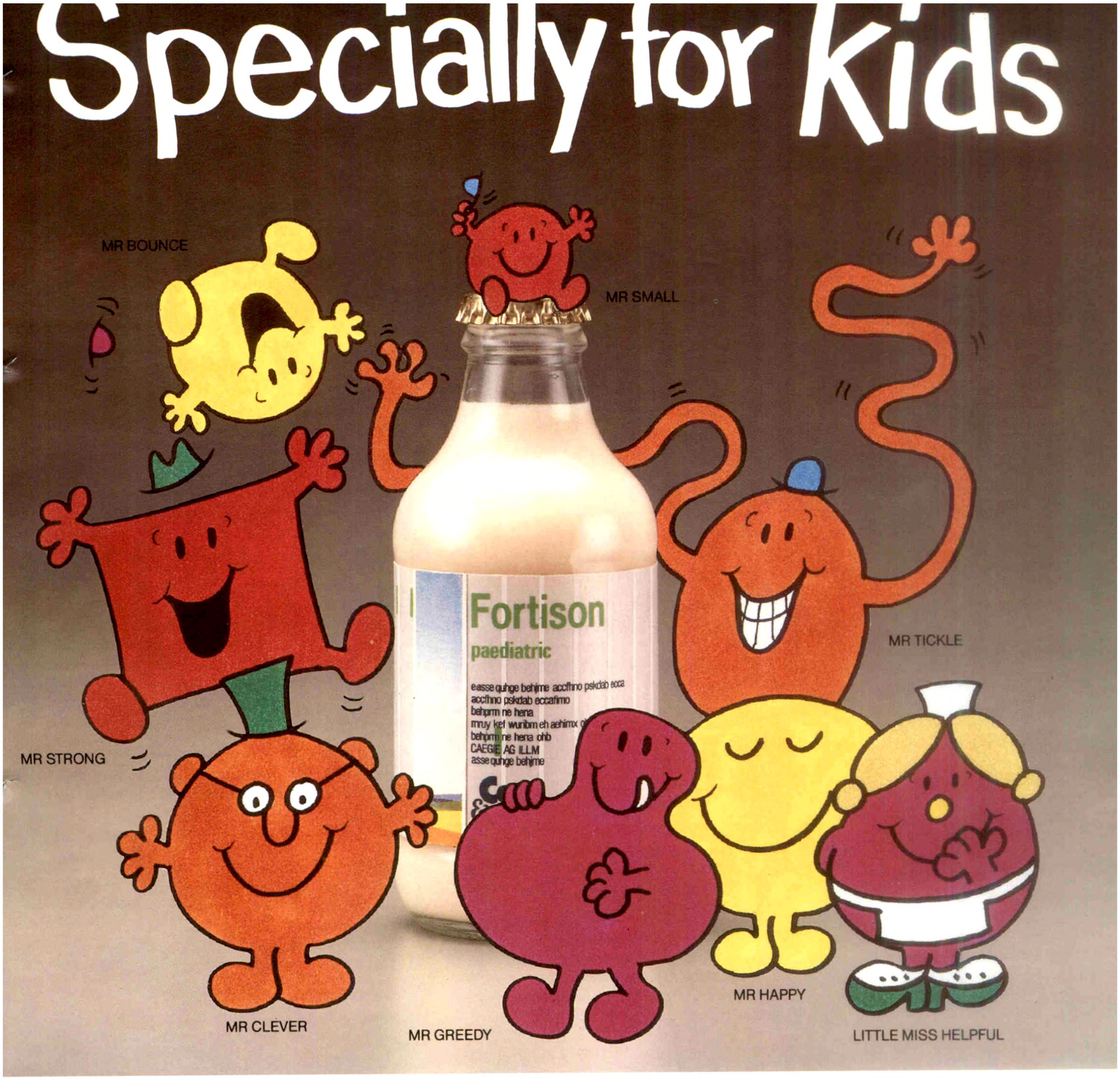

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[redacted]

Features and outcome in meningococcal disease presenting with maculopapular rash

O Marzouk, A P J Thomson, J A Sills, C A Hart, F Harris

Abstract

Sixty nine patients with meningococcal disease some of whom presented with a maculopapular rash were entered in a prospective multicentre study. The clinical and laboratory features of children presenting with maculopapular rashes were compared with those of children presenting with typical haemorrhagic rashes. Of the 69 children 26 (38%) developed maculopapular rashes; nine (13%) had a maculopapular rash only, and the remaining 17 had a mixed maculopapular-purpuric rash. Twelve of the 17 (7%) had less than 12 petechiae. Children with maculopapular rashes had significantly higher platelet counts (median 294 compared with 243×10^9/l), and plasma total haemolytic complement activity (80·5 compared with 65·0 U/ml) and significantly lower Glasgow meningococcal septicaemia prognostic scores (2·5 compared with 5·5) than those with purpuric rashes on admission. There were no significant differences between the groups in mortality, white cell count or absolute neutrophil count on admission, or C reactive protein concentration.

Meningococcal disease can present with a maculopapular rash alone but this does not necessarily mean that the disease is less severe.

The haemorrhagic rash seen in meningococcal disease is an important diagnostic and prognostic feature that varies in distribution and size from petechiae to ecchymoses.[1] There have been isolated case reports of meningococcal disease presenting with a maculopapular rash,[2 3] but the incidence has not been established in a prospective series.

In this prospective study we have compared the clinical and laboratory features and outcome of children who presented with maculopapular rashes with those of children who presented with classic rashes in meningococcal disease.

Patients and methods

During the year ending 14 November 1989, 69 consecutive children who presented at the Royal Liverpool Children's Hospitals (Alder Hey and Myrtle Street) and the paediatric units at Whiston, St Helens, Arrowe Park, and the Countess of Chester Hospitals with meningococcal disease were included in a prospective study.

On admission all children were seen by one of us (OM). A detailed account of the presenting illness, past medical history, and family history was obtained. All children were examined and a Glasgow meningococcal septicaemia prognostic score was estimated.[4]

Of the 69 cases, 53 were admitted because of the suspicion of meningococcal disease; 16 were not initially thought to have meningococcal disease and were included in the study later when meningococci were cultured from blood or cerebrospinal fluid.

Blood samples were collected at the time of admission. Full blood count including differential white cell and platelet counts were estimated by standard laboratory methods. Serum C reactive protein concentrations were estimated by laser nephelometry (Beckman Scientific Instruments Ltd). Samples of plasma were stored at −70°C before estimation of total haemolytic complement activity by a quantitative assay (Kallestad Laboratories, Quantiplate).

Bacteriological confirmation of the diagnosis was sought by standard Gram stain and culture of cerebrospinal fluid or blood, or both, either by the detection of meningococcal antigen in blood by latex agglutination and counter immunoelectrophoresis or in cerebrospinal fluid by latex agglutination (Wellcome Diagnostics).

Of the 69 cases, 54 were confirmed by one of the methods outlined above. A further six patients (all of whom had purpuric rashes) had abnormalities in the cerebrospinal fluid consistent with meningitis but had already been treated with antibiotics. These six were considered to have meningococcal disease giving a total of 60 confirmed cases. Each child who had a maculopapular rash alone was confirmed as having meningococcal disease on culture.

Nine other children, all of whom had typical purpuric rashes, were included on clinical grounds. In five children screening tests for meningococcal disease including examination of cerebrospinal fluid showed no evidence of meningococcal disease, but they had all been treated with antibiotics. Three had clinical evidence of meningitis but were considered too ill to have lumbar punctures on admission. One had no evidence of infection and no serological evidence of viral disease, but had a raised C reactive protein concentration.

Data were analysed with the Biostatistic Analysis Package (C Hetherington 1987) on a BBC B microcomputer. The Mann-Whitney U test was used to assess the significance of differences between groups.

Results

A total of 69 children were admitted with clinically suspected meningococcal disease, and in 60 it was confirmed by direct or indirect bacter-

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iological methods. Meningococci were cultured from all the children without rashes or whose only skin sign was a maculopapular rash.

Four children had meningitis but no rash. Twenty five had septicaemia without meningitis, and 24 of these had rashes. The remaining 40 children had both rashes and clinical evidence of meningitis (septicaemia and meningitis).

The children were classified according to the type of rash associated with their illness: maculopapular alone, petechial or purpuric, or both, mixed rash (both types), or no rash. The clinical and laboratory data are summarised in the table. There were 39 boys and 30 girls, a sex ratio of 1·3:1. Their ages ranged from 1 month to 14·5 years (median 18 months). There was no significant difference in age between children presenting with maculopapular rashes and those with other types of rash, but those children who did not develop a rash at any stage of their illness were significantly younger than those with classic purpuric rashes ($p<0\cdot05$) or mixed rashes ($p<0\cdot01$).

Nine children had maculopapular rashes alone. Seventeen had mixed rashes with both maculopapular and petechial or purpuric elements, and 38 had typical haemorrhagic rashes. Only five children did not develop a rash at any stage of their illness: four had meningitis and one had septicaemia.

Of the nine children who had maculopapular rashes alone, four had transient rashes that lasted for less than 24 hours after admission and in five the rashes persisted for up to three days after treatment had been started. Eight of these nine children had meningitis. The maculopapular rash was distributed on the trunk alone in six of the nine cases, on the trunk and extremities in two, and on the extremities alone in one (figure).

Sixty of the 69 children were feverish on admission including seven of the nine children who had maculopapular rashes alone; one of the remaining two became feverish after admission. The ninth patient was a teenager who although never feverish had headaches, vomiting, drowsiness, and double vision.

Children with maculopapular rashes had a significantly lower median Glasgow meningococcal septicaemia prognostic score ($p<0\cdot05$) and significantly higher median plasma haemolytic complement activity ($p<0\cdot05$) than those with purpuric rashes, but there was no difference between them and patients with any other type of rash. Children who had purpuric rashes on presentation had a significantly lower median platelet count than patients in any of the other groups (table).

Maculopapular rash associated with meningococcal disease.

There were no differences among the groups in C reactive protein concentration, total white cell or absolute neutrophil count on admission, or mortality.

Twelve children remained untreated for periods ranging from eight to 48 hours because the diagnosis of meningococcal disease was not considered. There were three in each of the four groups. The only death among these initially untreated patients had a mixed rash: the child had presented with a maculopapular rash that evolved eight hours later into an extensive purpuric rash.

Discussion

Previous reports of maculopapular rashes occurring in meningococcal disease have been of isolated cases[2] or in retrospective reviews.[3 5] In this prospective survey of meningococcal disease 64 children (93%) developed rashes during their illnesses; 26 children (38%) had maculopapular rashes with or without petechiae or purpura, and nine (13%) presented with maculopapular rashes alone. If we consider only those children in whom the disease was confirmed bacteriologically, the percentage of children with maculopapular rashes alone rises to 15%.

It has been suggested that meningococcal disease presenting with a maculopapular or petechial rash has a good prognosis and that the

Comparison of type of rash in meningococcal disease with clinical and laboratory variables

	Type of rash			
	Maculopapular (n=9)	*Purpuric (n=38)*	*Mixed (n=17)*	*No rash (n=5)*
Median age (months)	9	26·5	13	2
Median Glasgow meningococcal septicaemia prognostic score	2·5*	5·5*	3	Incomplete data
Median platelet count ($\times 10^9$/l)	294*	243*	299	338
Median haemolytic complement activity in plasma (CH50) (U/ml)	80·5*	65*	65	130
Median white cell count ($\times 10^9$/l)	16·3	14·8	19·9	9·1
Median neutrophil count ($\times 10^9$/l)	10·8	8·9	10·0	3·5
Median C reactive protein concentration (mg/l)	80	83	90	Incomplete data
No of deaths	0	5	1	0

*$p<0\cdot05$.

nature of the rash on admission could be used as a prognostic indicator.[5]

Maculopapular rash alone in meningococcal disease has, however, also been reported in fatal cases,[6] and it is possible that the delay in diagnosis of meningococcal disease with a maculopapular rash alone might contribute to mortality as these children are thought to have viral illnesses and are not started on antibiotic treatment.

In our series none of the children with a maculopapular rash alone died. There was only one child who presented with a maculopapular rash that later progressed to a typical purpuric rash. This girl was observed untreated for eight hours; when her rash was seen to contain some petechiae antibiotic treatment was started. Her rash progressed, she continued to deteriorate, and despite intensive support she died 36 hours after admission.

She had had no evidence of neck stiffness on admission and a low white cell count with relative neutropenia, both of which are poor prognostic factors in typical meningococcal disease.[7–10] It seems that the same poor prognostic factors apply when children with meningococcal disease present with maculopapular as with any other type of rash. The changing nature and evolution of the rash in meningococcal disease in this child emphasises the need to review children after admission and to report any changes in the nature of the rash.

Platelet count and plasma total haemolytic complement activity were the only laboratory variables that differed significantly between children presenting with maculopapular and purpuric rashes. Thrombocytopenia with or without disseminated intravascular coagulation is a poor prognostic factor,[10 11] and low haemolytic complement activity in plasma has been associated with rapidly progressive meningococcal disease.[12]

It must be noted, however, that despite the significance of the difference in platelet counts and haemolytic complement activity these median values are all within the normal reference range. Children with maculopapular rashes had a significantly lower median Glasgow meningococcal septicaemia prognostic score than those presenting with purpuric rashes. This difference is not entirely explicable on the basis of the different types of rash, because an extending, ecchymotic, or extensive purpuric rash contributes only one point out of a total of 15 on the prognostic score.

Differentiating the maculopapular rash or meningococcal disease from that of a viral infection remains a problem. Diagnosis before haemorrhagic elements develop would permit earlier treatment.

Laboratory variables such as C reactive protein concentration may be helpful in supporting the diagnosis, but ultimately bearing the diagnosis in mind when attending a feverish child with a rash is of great importance.

One striking point in the history of the maculopapular rash in meningococcal disease is its rapid evolution. If this is important it could be the only clue on admission that would enable a clinical differentiation to be made between the maculopapular rash of meningococcal disease and that of non-specific viral disease. A prospective study to answer this question is in progress.

Careful examination of feverish children with rashes is important. Of the 17 children in our series who had mixed rashes, 12 (71%) had only a few haemorrhagic spots (less than 12) within a predominantly maculopapular rash.

In this study the only child whose rash evolved from being only maculopapular to include haemorrhagic elements died. Her rash evolved eight hours after admission. This is consistent with other such reported cases in which the rash usually evolved within 24 hours of admission.[3 6] During this critical first 24 hours close observation of the rash and regular application of the Glasgow meningococcal septicaemia prognostic score to detect changes in clinical condition may help to prevent such deaths.

In summary, this is the first prospective study to our knowledge to establish the incidence of meningococcal disease presenting with a maculopapular rash alone. This occurred in nine children (13% of all cases and 15% of confirmed cases), while 17 (25%) had mixed maculopapular and haemorrhagic rashes.

Despite its benign appearance the maculopapular rash can still herald a potentially fatal disease. Meningococcal disease must be considered in the differential diagnosis of any feverish child with a maculopapular rash.

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Breast feeding and protection against neonatal sepsis in a high risk population

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Abstract

Protection against neonatal sepsis by breast feeding was investigated in a developing community. A case-control study was carried out with 42 cases from a hospital and 270 controls, matched for age and socioeconomic conditions from the community. Exclusive breast feeding was extremely rare, most babies being partially breast fed and a few being given formula feed or animal milk.

A highly significant odds ratio of 18 was obtained, showing that even partial breast feeding protects against neonatal sepsis in such a population.

Neonatal sepsis is a major cause of morbidity and mortality among young infants. In developed countries the incidence of neonatal sepsis is about 3/1000 live births.[1 2] A comparable figure for Pakistan is not available, but it should be higher as infections are the main cause of neonatal mortality there. A study from Mayo Hospital, Lahore, showed that cases of neonatal sepsis comprised 30% of the total neonates admitted with infections.[3] Mortality in neonatal septicaemia remains high, 45% being reported from Saudi Arabia[4] and 12% from Sweden.[5] In an ongoing longitudinal study of children in Lahore, Pakistan, the initial estimates suggest that of the total deaths in the neonatal period 12% are the result of neonatal sepsis (unpublished data). In this population, breast feeding is not usually initiated before 48–120 hours after birth and certain other food and fluids are fed instead.[6] These foods and fluids are often contaminated with bacteria, mainly Gram negative (I Alderberth and K Khalil, personal communication).

A study from Sweden suggested that breast milk protects against neonatal septicaemia and meningitis caused by Gram negative bacteria.[7] We undertook a case-control study in a high risk population in Lahore, Pakistan to find out if breast feeding can protect against neonatal sepsis.

Patients and methods

STUDY GROUPS

A matched case-control study was carried out with 42 cases of neonatal sepsis that had been admitted to hospital and 270 controls selected from the community in Lahore, Pakistan.

The cases (3–28 days old) were consecutive patients admitted to hospital with a diagnosis of septicaemia from January to August 1987. Nine cases were 3–7 days old when admitted and had become ill at the ages of 3, 3, 3, 4, 4, 5, 5, 6, and 7 days. The other 33 had become ill and were admitted when they were aged 8–28 days. Those included were severely ill term neonates admitted to the nursery of the Mayo Hospital, Lahore, with a clinical diagnosis of septicaemia based on three or more of the following features: hypothermia or hyperpyrexia, hypotonia, lethargy, refusal to feed, and jaundice or signs of meningeal irritation, or both. Neonates with severe infectious diseases such as pyoderma, diarrhoea, or radiologically diagnosed bronchopneumonia were excluded, as were premature infants, twins, babies with congenital malformations, and asphyxiated neonates. The provisional diagnosis was always confirmed by the senior consultants. Because antibiotic treatment had often been instituted before admission and the cultures that had been done were not of a high enough quality to ensure scientific reliability, the results of the blood cultures have not been considered.

The controls were identified within the community and were of the same socioeconomic group as the cases. The controls were neonates without apparent infection, identified from the community birth registers within one to two weeks after a case had been admitted (with a maximum difference in the date at birth of seven days), controlling for differences in the mode of feeding in relation to the season of the year.[8] We aimed to select eight controls for each case matching for area of living and date of birth to within seven days. The number of controls found, however, was less than expected. The mean number of controls for each case was 6·4 (range 4–8), as it was not always possible to find eight infants with matching birth dates. We did not regard hospital patients as suitable controls as only extremely ill infants are referred or directly admitted. Most of them have been ill for several days or have various anomalies that would militate against them being breast fed.

The mothers were interviewed by trained health workers who were unaware of the objective of the study, using the same standardised questionnaire for both cases and controls. Risk factors such as sex, birth order, place of delivery, qualification of birth attendant, interval between rupture of membranes and delivery, and techniques of cord care, were recorded. A detailed retrospective history of feeding, starting from the day of birth (including frequency of breast feeding) was also recorded. The pattern that evolved was classified into three groups: exclusive breast feeding; partial breast feeding—that is, those who started breast feeding after or in addition to giving any other foods and fluids such as water or fresh animal milk; and no breast feeding—these infants were given commercial formula feeds or fresh animal milk.

The frequency of nursing during day and night was recorded both for cases and controls, but was difficult to evaluate for the cases because of their severe disease. As a result of this, the amount of breast milk received by the partially breast fed infants is unknown.

STATISTICAL ANALYSIS

Statistical evaluation was by unmatched analysis for case-control studies, and odds ratios were calculated. Unmatched analysis was used because of the unequal number of controls/case, Mantel and Haenszel's χ^2 with one degree of freedom was used for calculation of the significance of differences. Woolf's limits were applied when estimating 95% confidence intervals (CI).[9] A test for homogeneity was done after stratifying the various risk factors.[10]

Results

No significant differences were found between the cases and controls for age, sex, birth order, place of delivery, qualification of birth attendant, interval between rupture of membranes and delivery, sterilisation of instruments used, or handling, cutting, and further care of the cord (table 1). The mode of feeding, however, differed between the cases and controls. The only exclusively breast fed baby, in the control group, was included in the study. In the partially breast fed group there were 19 cases and 253 controls (table 2). In the group that was given no breast milk there were 23 cases and 17 controls. The incidence of breast feeding was less among the cases than the controls, with an odds ratio of 18. The odds ratio did not vary significantly when the data were stratified for sex, birth order, place of delivery, and qualification of the birth attendant, or instruments used (data not shown).

Table 1 Comparison of variables in which there was no significant difference between cases of neonatal sepsis and controls. Values are given as number (%)

	Cases of neonatal sepsis (n=42)	*Controls (n=270)*
Age (0–28 days):		
Mean	14·8	15·7
Median	14	16
Sex:		
Male	24 (57)	149 (55)
Female	18 (43)	121 (45)
Median birth order (1–10)	3	3
Place of delivery:		
Hospital	14 (33)	90 (33)
Home	28 (67)	180 (67)
Birth attendant:		
Doctor	12 (29)	92 (34)
Qualified midwife	22 (52)	154 (57)
Untrained midwife	8 (19)	24 (9)
Mode of delivery:		
Spontaneous	40 (95)	248 (92)
Forceps	1 (2)	14 (5)
Caesarean	1 (2)	8 (3)
Time between rupture of membranes and delivery:		
0–24 Hours	41 (98)	260 (96)
>24 Hours	1 (2)	10 (4)
Instruments used for delivery:		
Sterilised	24 (57)	124 (46)
Unsterilised	18 (43)	146 (54)
Tying of cord:		
Clamp	10 (24)	65 (24)
Sterilised thread	7 (17)	72 (27)
Unsterilised thread	25 (60)	133 (49)
Care of cord:		
Spirit/gentian voilet	5 (12)	33 (12)
Antibiotics	14 (33)	96 (36)
Oil or butter	15 (36)	108 (40)
Ash	0	2 (1)
Nothing	8 (19)	31 (12)

Table 2 Occurrence of sepsis and mode of feeding

	No (%) of cases of neonatal sepsis	*No (%) of controls*	χ^2	*p Value*
Animal milk or formula	23 (55)	17 (6)	71·8	<0·001**
Partial breast feeding	19 (45)	253 (94)*		
Total	42	270		

*The single exclusively breast fed infant was included here.
*Odds ratio 18 (95% CI 7·9 to 37·7 using Wolf's limits).

Discussion

This study indicates that protection against neonatal sepsis is given even with partial breast feeding among neonates in a poor community with a high mortality from neonatal sepsis.

In these severely ill infants the diagnosis was usually obvious and there were few differential diagnoses. This was especially true because no case of early neonatal sepsis, which can be difficult to diagnose, was seen in this study. It is possible that early cases of neonatal sepsis died at home before they had time to reach hospital.

The septicaemic infants were not less likely to be breast fed than the controls. This is based on our findings that in the study area 98% of those that are going to be breast fed have started breast feeding on or before day 3 and all are being breast fed by day 5.[6] In 39 of the 42 cases, the onset of septicaemia was after day 4, and only three presented on day 3.

Not only was exclusive breast feeding uncommon in the community that we studied but colostrum was rarely fed. Instead, various other—often infected—foods and fluids were given. This may explain why the intestinal tracts of neonates in the study area were colonised with aerobic Gram negative bacteria significantly earlier than those of Swedish infants.[11] In addition, the early aerobic gut flora of Pakistani infants contained bacteria of more genera compared with those of Swedish infants. Klebsiella, enterobacter and citrobacter were also significantly more common among the non-breast fed Pakistani infants than among those that had early breast feeding. This early exposure to various bacterial strains might result in an unstable and potentially pathogenic gut flora that causes early infections such as neonatal sepsis and diarrhoea, which are common in this community. It is possible that the early microbial exposure and lack of feeding with colostrum could cause the severe cases.

Although the events at the time of delivery like mode of delivery, and risk factors such as sex, birth order, place of delivery, qualification of birth attendant, interval between rupture of membranes and delivery, and techniques of cord care were evenly distributed among both cases and controls, there was a significant difference between the groups in the mode of feeding. The study includes unequal numbers of controls for each case because of the preset matching criteria that were used. There is no reason to believe that cases with more controls are different from those with fewer controls with regard to background measures of importance. We have not tested this statistically because the lowest number of controls selected for any one case was four. If exactly four of the controls were selected for each case, the total number of controls would be 168. Theoretically, all the deleted controls (n=102) could belong to the partial breast fed group (table 2). Seventeen of the controls would then still not be breast fed, but 'only' 151, or 89%, would be partially breast fed. In this extreme situation the odds ratio is 10·8 ($p<0·001$) and the conclusion of the study would thus not be influenced.

Of the total cases, 45% were partially breast fed compared with 94% of the controls, so this study shows that even partial breast feeding can protect infants from neonatal sepsis. Possibly exclusive breast feeding would provide even better protection. In developing countries, therefore, exclusive breast feeding (including early colostrum feeding) should be promoted by teaching birth attendants and giving information to the family.

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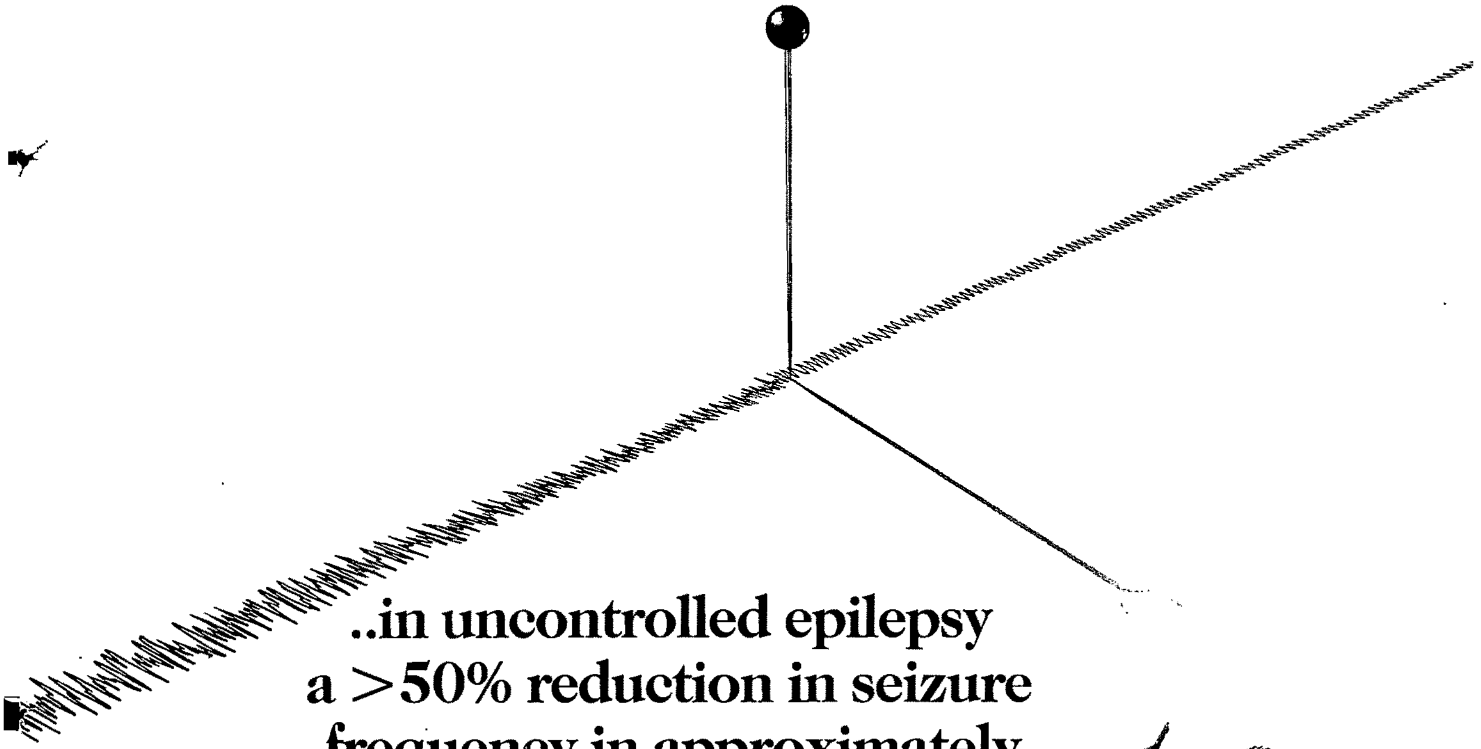

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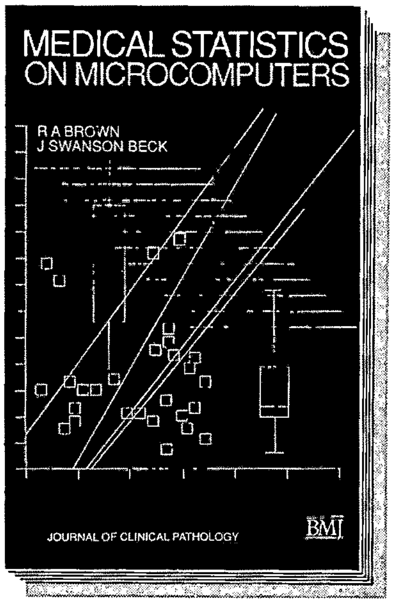
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Screening of diabetic children for coeliac disease with antigliadin antibodies and HLA typing

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Abstract

IgA and IgG antigliadin antibodies were measured in 498 patients with insulin dependent diabetes mellitus and no history of intestinal malabsorption. Thirty patients had abnormal concentrations of antigliadin antibodies; 22 of these had an intestinal biopsy carried out and 16 of the 22 had subtotal villous atrophy suggestive of coeliac disease (prevalence 3·2%). There were no significant differences between patients with coeliac disease and diabetes and diabetic patients with normal IgA antigliadin antibodies in any of the nutritional variables measured, duration of diabetes, and mean insulin requirement. The mean age of onset of diabetes and attainment of expected height for age were both significantly lower in the patients with both diseases. Typing HLA classes I and II was done in 242 patients. The incidence of HLA-B8, DR3, and DQW2, which are commonly associated with both the diseases, is increased when both are present.

Coeliac disease is more common among patients with insulin dependent diabetes mellitus than among the general population. The estimated incidence among normal children in Europe varies from 1:500 to 1:3000,[1–7] compared with that among diabetic children, which is reported to be between 0·97% and 3·5%[8–15]

Measurement of IgA and IgG antigliadin antibodies in serum using a method with a sensitivity of over 90%,[16–18] has allowed the identification of oligosymptomatic forms (the most common symptoms are low height and weight for age) and asymptomatic forms of coeliac disease.[17 19–22] Screening of children with diabetes for coeliac disease using antigliadin antibodies, has therefore been widely adopted in clinical practice.

Previous studies of genetic[23–25] and immunogenetic aspects,[26–29] and the finding of increased HLA-DR expression on intestinal epithelial cells and pancreatic β cell surfaces in both diabetes and coeliac disease, suggest a common pathogenesis for tissue damage in both diseases.[30 31]

The aims of this study were: to screen children with insulin dependent diabetes for coeliac disease using measurement of antigliadin antibodies, and to identify more detailed HLA associations with both diseases.

Patients and methods

Six centres of paediatric diabetology (Bari, Milan, Naples, Pisa, Turin, and Trieste), which are representative of the Italian paediatric population according to geographical distribution and ethnic background, took part in the study. We studied 498 patients with insulin dependent diabetes mellitus (227 girls, 271 boys; mean age 12·7 years, range 1·1–27·6) at the onset of their diabetes and at follow up visits between August 1987 and April 1988. The mean duration of diabetes was 5·5 years (range 0–20·7) and the mean age at diagnosis was 7·2 years (range 0·3–20·2). None of the patients studied had a history of intestinal malabsorption.

The following clinical and laboratory data were evaluated: age, weight, and height (centile for age), age of onset of diabetes, duration of the illness and insulin requirement, gastrointestinal history, haemoglobin, serum iron and total serum IgA immunoglobulin concentrations (the values were compared with reference ranges for age[32]), one hour xylose test,[33] and IgA and IgG antigliadin antibody concentrations. These assays were carried out in a single centre, using the enzyme linked immunosorbent assay (ELISA) indirect method (double layer).[34] The reference range was calculated on a population of 50 healthy children; the values of the examined samples were calculated as percentages of absorbance with regard to a reference serum pool of positive antigliadin antibodies. Values of antigliadin antibodies more than two standard deviations above the mean were considered abnormal.

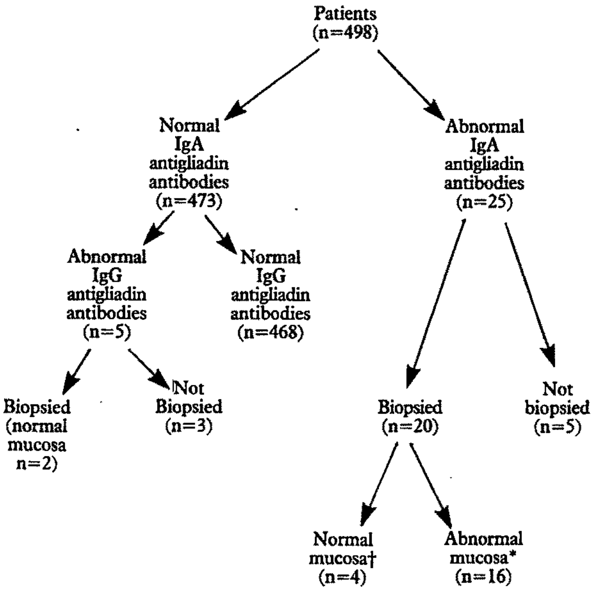
The intestinal biopsy specimens were obtained with a suction capsule and examined histologically.[35] Typing of HLA histocompatibility antigens class I (A, B, and C) and class II (DR-DQ) were carried out at the individual centres in 242 subjects.[36 37] The incidence of the HLA antigens among the subjects studied was compared with that in healthy control groups (800 blood donors from immunohaematology divisions, National Insitute of Cancer, Milan) and with a control group of 26 nondiabetic coeliac patients (mean age 11·1 years, range 1·5–17·9).

The statistical analysis was carried out with Student's *t* test, the χ^2 test for independent samples, and the χ^2 test with Yates's correction. The p value was multiplied by the number of tested antigens to generate the p×n value. The data from the various centres were comparable.

Results

Abnormal concentrations of IgA antigliadin antibodies were found in 25 of the 498 patients studied (5%) (table 1). Twenty of these 25

Table 1 Results of the screening tests with IgA and IgG antigliadin antibodies in the 498 patients with diabetes mellitus type 1


Patients (n=498)
Normal IgA antigliadin antibodies (n=473)
Abnormal IgA antigliadin antibodies (n=25)
Abnormal IgG antigliadin antibodies (n=5)
Normal IgG antigliadin antibodies (n=468)
Biopsied (normal mucosa n=2)
Not Biopsied (n=3)
Biopsied (n=20)
Not biopsied (n=5)
Normal mucosa† (n=4)
Abnormal mucosa* (n=16)

*IgG antigliadin antibodies abnormal in nine and normal in seven.
†IgG antigliadin antibodies normal in all.

(80%) underwent an intestinal biopsy, and we found subtotal villous atrophy in 16 subjects (3·2%). Nine of these 16 patients had abnormal concentrations of IgG antigliadin antibodies.

IgG antigliadin antibodies concentrations were abnormal in 14 of the 498 patients (3%); nine also had abnormal concentrations of IgA antigliadin antibodies, associated with subtotal villous atrophy. Two of five patients with abnormal concentrations of IgG antigliadin antibodies and normal IgA antigliadin antibodies underwent intestinal biopsy and the mucosa was histologically normal in both.

The antigliadin antibodies concentrations in patients with mucosal changes reverted to normal after a year on a gluten free diet, and in five subjects who underwent a second biopsy the mucosa had also completely recovered.

Table 2 Comparison of main nutritional variables among patients screened with IgA antigliadin antibodies

	IgA antigliadin antibodies		
	*Abnormal** (n=25)		Normal (n=473)
	Abnormal mucosa (n=16)	Normal mucosa (n=4)	
Abnormal IgG antigliadin antibodies	9	0	5
Abnormal xylose test	4	2	92
Anaemia	0	1	5
Iron deficiency	2	3	44

*Five subjects not biopsied.

Data on xylose tests, iron deficiency and anaemia are given in table 2.

There were no significant differences between patients with coeliac disease and diabetes and diabetic subjects with normal IgA antigliadin antibodies with regard to weight, duration of diabetes, and insulin requirements (table 3). Height, mean age at onset of diabetes and gastrointestinal history were significantly different between the two groups of patients ($p<0·01$).

The incidence of the HLA antigens found in the group of 242 diabetic patients, in the group of patients with diabetes and coeliac disease (n=16), and in the control group (n=800) were compared. Compared with the controls the diabetic subjects had a significantly higher incidence of the antigens HLA-A9, CW7, B8, B18, DR3, DR4, DQW2, and DQW3, and a lower incidence of the antigens HLA-DR2 and DR7. A detailed table is available from the author.

The incidence of the HLA antigens in the diabetic patients with normal concentrations of IgA antigliadin antibodies (n=210) and in those with both coeliac disease and diabetes (n=16) were compared with each other and with a control group made up of 26 patients with coeliac disease. In the patients with both coeliac disease and diabetes the incidence of the HLA A28, B8, B17, and DR3 was significantly higher than in the patients with diabetes alone, while antigen B18 was less common. When compared with the group with coeliac disease alone, the group with both diseases showed an increase in the DR5 antigen and a reduction in the DR7 and DR11 antigens. These differences were, however, not confirmed statistically when the 'p' value was multiplied by the number of tested antigens (p×n).

The comparative evaluation between the non-coeliac diabetic patients and the control group with coeliac disease alone showed the preponderance of the CW4, DR4, and DR5 antigens in the first group, while the coeliac controls had a higher incidence of A24, A26, A30, DR7, DR11, and DQW2 antigens. A detailed table is available from the authors.

Discussion

The results of this multicentre study confirm previous reports (table 4) that there is a higher prevalence of coeliac disease in young patients affected by diabetes mellitus type I (3·2%). This

Table 3 Comparison of auxological and clinical data between diabetic patients with normal IgA antigliadin antibodies and diabetic coeliac patients

	Abnormal IgA antigliadin antibodies, abnormal biopsy specimen (n=16)	*Normal IgA antigliadin antibodies (n=466)*	*p Value*
No (%) with height ≤3rd centile	5 (31)	30 (6)	<0·01
No (%) with weight ≤3rd centile	2 (13)	25 (5)	NS
Mean (range) duration insulin dependent diabetes mellitus: (years)	6·5 (0·9–14·8)	5·4 (0–20·7)	NS
Mean (SD) age at onset of diabetes (years)	4 (2·9)	7·2 (3·6)	<0·01
Mean insulin requirement (U/kg)	0·9	0·83	NS
No (%) gastrointestinal symptoms	9 (56)	48 (10)	<0·01

Table 4 Reported prevalence of coeliac disease in children with insulin dependent diabetes mellitus

First author and reference	*No of patients with insulin dependent diabetes mellitus evaluated*	*No of patients with coeliac disease identified*	*Reported prevalence*
Visakorpi[8]	?	5	1
Thain *et al*[9]	400	6	1·5
Maki *et al*[10]	215	4	2·3
Savilahti *et al*[11]	201	7	3·5
Cacciari *et al*[13]	146	5	3·4
Koletzko *et al*[15]	1032	10–20	0·97–1·94

figure is probably an underestimate, as not all the patients with abnormal values of IgA antigliadin antibodies underwent intestinal biopsy. The assay of serum IgA antigliadin antibodies resulted in a test with greater sensitivity than specificity because of the high number of false positives (four in 20 of the subjects biopsied).

The measurement of IgG antigliadin antibodies seems to be less sensitive, as the test was negative in seven of 16 known coeliac patients (44%). The fact that the intestinal mucosa was normal in the two patients with high concentrations of IgG antigliadin antibodies and normal IgA antigliadin antibodies further emphasises the lack of specificity of the test.

In addition, our results show the unreliability of the one hour xylose test; the number of false negatives was high (62·5% of coeliac patients) as was that of the false positives (19·7%).

We confirmed that in patients with both diabetes and coeliac disease the mean age of onset of the diabetes was significantly lower than in the patients with diabetes alone.[15] The onset of the coeliac disease did not seem to have any connection with the duration of the diabetes. None of the patients tested at the onset of diabetes showed a transitory rise in antigliadin antibodies concentrations, contrary to other reports.[12 13 15]

In patients with coeliac disease and diabetes a high incidence of previous gastrointestinal symptoms was found (56%), although only three of them had any complaints at the time that the coeliac disease was diagnosed. Moreover, subjects with mucosal changes had no significant differences in nutritional variables and in insulin requirements compared with the other diabetic patients.[11 13]

In our experience short stature is the main clinical finding in patients with both coeliac disease and diabetes; although coeliac disease is a well established cause of growth retardation it has not been described previously in patients with both diseases.[17 19–22]

Our data confirm that all diabetic children should be screened for coeliac disease, particularly if they have stunted growth. Of the available screening tests, measurement of antigliadin antibodies is the test of choice.[11–13]

The onset of coeliac disease in diabetic patients does not seem from our study and from previous reports to affect metabolic control of diabetes, and little is known about the onset of nutritional deficits in untreated patients with few or no symptoms.[11 13] The main goal of a gluten free diet in patients with both diseases, therefore, should be the prevention of short stature, even if the final height of patients with coeliac disease is influenced mainly by genetic characteristics.[38] It has been proposed that a strict gluten free diet may lower the increased risk of patients with coeliac disease of developing intestinal malignancies,[39] but this question remains controversial.[40]

The study of the HLA histocompatibility antigens confirms that in our diabetic population, in comparison with the healthy population, antigens B8, DR3 and DR4 are more common, as previously reported, and antigens A9, CW7, DQW2, and DQW3 are also more common, though they are rarely described in association with diabetes. Our evaluation gives further evidence for the protective role of HLA antigens DR2 and DR7 in diabetes.[41 42] The evaluation of HLA antigens in the 16 patients affected by both diabetes and coeliac disease, compared with the control group, confirms the higher incidence of characteristic antigens of both diseases (B8, DR3 and DQW2), with relative risks of 8·4 for the B8, 20 for the DR3, and 7·5 for the DQW2.

The higher incidence of the HLA antigens B8 and DR3 in the group of patients with both coeliac disease and diabetes compared with the non-coeliac diabetic subjects supports a pathogenetic role for an immune response mechanism. These antigens could be in 'linkage disequilibrium' with the immune response genes, and in some way they represent markers of autoimmunity.

To confirm this, these antigens are more common among the group of patients with both diseases; moreover, in these patients the onset of diabetes is significantly earlier ($p<0·01$). This suggests a major autoimmune reactivity in the subjects carrying these HLA antigens. The HLA marker that characterises the association of diabetes and coeliac disease seems to be linked with the antigen DR3.

We thank Dr Proverbio Maria Carla and Mrs Puzzovio Maria for doing the antigliadin antibody measurements, without whom this study would not have been possible.

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Novel experience

The *Drug and Therapeutics Bulletin* is an excellent publication to which we can all look for sound therapeutic advice. Commenting on vigabatrin, however (*Drug and Therapeutics Bulletin* 1990;28:95–6), it has come up with an interesting suggestion which could have more general application. 'Treatment should be started', it says, 'by clinicians experienced in its use'. What astute advice about a new drug! 'Were you experienced in the use of this drug, doctor?' 'No, m'lud'. 'Why not?' 'It was new, m'lud'.

The incidence of adverse effects from new drugs can be cut 'at a stroke' by making sure that almost nobody can prescribe them, just as making it illegal to drive a car unless you have driven one before would solve the road traffic problem completely over the next 50 years or so. Or perhaps we could abolish the divorce courts by insisting that only the nuptially experienced should be allowed to marry.

It is sensible to suggest that in the early days most new drugs should be prescribed by doctors who have a large experience of treating the condition for which the drug is to be used. But there's always a first time for all of us.

ARCHIVIST

Archives of Disease in Childhood 1991; **66:** 495–500

Energy content of stools in normal healthy controls and patients with cystic fibrosis

J L Murphy, S A Wootton, S A Bond, A A Jackson

Abstract

Stool energy losses and the sources of energy within the stool were determined in 20 healthy controls and 20 patients with cystic fibrosis while on their habitual pancreatic enzyme replacement treatment. Stool energy losses were equivalent to 3·5% of gross energy intake in healthy children (range 1·3–5·8%). Despite a comparable gross energy intake, stool energy losses were three times greater in patients with cystic fibrosis than controls averaging 10·6% of gross energy intake (range 4·9–19·7%). Stool lipid could account for only 29% and 41% of the energy within the stool in controls and patients with cystic fibrosis respectively and was poorly related to stool energy. Approximately 30% of the energy within the stool could be attributable to colonic bacteria in both the healthy children and patients with cystic fibrosis. These results suggest that stool energy losses in healthy children are relatively modest but that even when patients with cystic fibrosis are symptomatically well controlled on pancreatic enzyme replacement, raised stool energy losses may continue to contribute towards an energy deficit sufficient to limit growth in cystic fibrosis. As the energy content per gram wet weight remains relatively constant (8 kJ/g), stool energy losses may be estimated from simple measurements of stool wet weight.

The amount of energy within the stool each day in healthy adults is generally believed to be equivalent to approximately 5% of the gross energy intake.[1] As stool energy losses appear to be relatively small and the collection and analysis of faecal material is both time consuming and unpleasant, the potential contribution that stool energy losses may make in limiting the availability of energy from the diet is often overlooked. To our knowledge, there have been no studies that have been specifically conducted to determine the magnitude of stool energy losses in children aged between 5–16 years. Our understanding of both the magnitude and origins of energy within the stool in normal healthy children and diseased states in childhood is limited. Further studies are required to determine whether stool energy losses may limit the availability of energy from the diet and thereby restrict growth.

One disease where the maldigestion and malabsorption of lipid, protein, and carbohydrate may limit the availability of energy from the diet resulting in restricted growth is cystic fibrosis.[2] The standard approach to the management of the gastrointestinal problems associated with cystic fibrosis has been exogenous pancreatic enzyme replacement treatment. In clinical practice, enzyme replacement is primarily directed towards the symptomatic correction of steatorrhoea, abdominal pain relief, and the reduction in stool frequency and stool mass passed each day. Of these, steatorrhoea would appear to be the most important clinical consideration and has frequently been used as an index of the extent of maldigestion.[3 4] Using this empirical approach it is commonly assumed that when the gastrointestinal symptoms and steatorrhoea are improved, the amount of energy available from the diet would be normal. However, the extent to which stool energy losses are completely normalised in patients with cystic fibrosis on their habitual established enzyme replacement has not been determined.

Therefore the aim of this study was to determine the amount of energy within the stools each day in normal healthy children and in patients with cystic fibrosis who believed themselves to be comparatively asymptomatic on their habitual pancreatic enzyme replacement treatment.

Patients and methods

Twenty normal healthy children aged 6–11 years (mean 9·4 years) from a local school participated in the study. Twenty patients with cystic fibrosis aged 5–25 years (mean 11·4 years) from a cystic fibrosis clinic in the Wessex region were also studied on their normal established pancreatic enzyme replacement therapy. Subject details are shown in the table. The patients with cystic fibrosis were taking between 11–43 (mean 22) capsules of pancreatin (Creon, Duphar: 8000 BP units lipase/capsule) each day and had been taking the enzyme in the form of enteric coated microspheres for at least one year before the study. All of the patients self titrated their enzyme dosage against gastrointestinal symptoms including abdominal pain, diarrhoea, offensive bulky stools, and increased stool frequency. No attempt was made to alter or intervene with the management of the enzyme replacement therapy. Informed consent was obtained from all of the subjects and the study protocol was approved by the ethical committee of Southampton and South West Hampshire Health Authority.

Weighed food intake was recorded for a period of seven days in a standard manner as described by Marr[5] using digital electronic

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Details of the normal healthy controls and patients with cystic fibrosis including stool energy losses and gross energy intake

Subject No	*Age (years)*	*Sex*	*Weight (kg)*	*Height (cm)*	*Gross energy (kJ/day)*	*Stool energy (kJ/day)*	*Pancreatic enzyme replacement treatment (capsules /day)*
				Controls			
1	6·4	F	25·4	124·7	8690	191	—
2	8·7	F	30·9	134·9	8808	363	—
3	9·9	M	30·3	144·2	7306	355	—
4	9·9	F	25·3	139·6	7412	160	—
5	8·1	F	25·5	129·5	8710	169	—
6	8·1	M	27·6	128·8	8951	186	—
7	11·0	F	35·0	138·9	8807	268	—
8	10·2	M	25·0	133·8	10621	412	—
9	11·1	F	36·4	142·0	9865	271	—
10	11·1	F	47·3	146·4	11191	647	—
11	7·5	M	25·4	135·7	9609	446	—
12	8·4	F	28·6	134·1	9152	123	—
13	9·7	M	33·5	136·4	10108	242	—
14	10·4	M	38·1	147·7	9179	525	—
15	7·6	M	25·8	131·5	7698	294	—
16	10·7	F	38·4	152·6	10438	506	—
17	10·3	M	35·1	148·8	10803	301	—
18	8·3	F	30·9	139·5	9051	288	—
19	11·0	M	35·4	138·7	10379	458	—
20	10·1	M	36·3	145·3	12492	530	—
Mean (SEM)	9·4 (0·3)		31·8 (1·3)	138·7 (1·6)	9464 (292)	337 (33)	
			Patients with cystic fibrosis				
1	6·9	F	20·4	118·6	10580	2084	30
2	13·8	F	26·5	142·0	10752	1092	37
3	7·9	F	28·1	128·9	10831	1058	20
4	8·9	M	34·2	131·8	9589	850	11
5	17·4	F	38·9	154·0	5904	716	23
6	10·2	F	21·8	133·0	5652	383	20
7	22·9	M	45·3	159·9	9853	1020	12
8	14·9	M	53·2	166·9	14755	1504	30
9	9·5	M	29·5	132·6	8558	1224	9
10	9·0	F	28·0	131·2	8371	1414	19
11	18·0	F	43·3	155·0	5771	963	15
12	5·3	M	20·0	112·8	5895	493	27
13	8·5	F	24·8	133·2	13954	944	14
14	5·5	M	17·5	108·5	6632	767	16
15	5·4	F	18·3	113·4	11689	575	43
16	5·8	F	18·0	109·1	7285	539	16
17	8·1	F	34·0	135·0	11389	1152	24
18	6·3	F	20·0	114·2	7763	1134	25
19	17·4	M	58·9	175·1	15907	898	15
20	25·7	F	44·0	165·3	17543	1014	23
Mean (SEM)	11·4 (1·4)		31·2 (2·8)	136·0 (4·6)	9934 (787)	991 (87)	22 (1·9)
Significance	NS		NS	NS	NS	$p<0·0001$	—

NS, not significant.

scales (Hanson). The families of the subjects were instructed in the use of the scales and the recording of food intake before commencing the study. They were closely monitored and given support throughout the study period. After completion of the record, the family was interviewed to ensure that there were no omissions or errors. The diaries were coded according to the McCance and Widdowson food tables[6] with additional data from the supplements to the food tables[7] [8] [9] and manufacturers' information. The weighed food intake was analysed using a computerised food composition database (MicroDiet, University of Salford). Gross energy intakes were estimated by multiplying the intakes of lipid (39·3 kJ/g), protein (as nitrogen×6·25; 23·6 kJ/g), carbohydrate (17·4 kJ/g) and dietary non-starch polysaccharide (17·4 kJ/g) by their respective heats of combustion values.[10]

All stools were collected for the final three days between carmine markers. The stools were collected into polyethylene bags and immediately frozen. All the stool collections were complete. All of the subjects were cooperative, willing, and capable of following the details of the procedure. At no time was difficulty encountered nor any need found for modification of the procedure to accommodate the subjects. The pooled three day stools were weighed and homogenised with distilled water. Aliquots were then freeze dried overnight (Genevac) to a constant weight.

The Gompertz and Sammons modification[11] of the method of Van de Kamer *et al*[12] was employed to measure the lipid content of the wet stool. Total nitrogen analysis was performed by an automated Kjeldahl technique (Tecator) on a sample of the wet stool. The energy content of the stool was measured by ballistic bomb calorimetry[13] (Gallenkamp) on a sample of freeze dried stool. The bacterial content of the dried stool was determined by repeated fractional centrifugation using the method developed by Stephen and Cummings.[14] A freeze dried stool sample was resuspended in formylsaline and 10% sodium lauryl sulphate. The amount of bacteria within the bacterial fraction was confirmed by phase contrast microscopy using a haemocytometer (Weber Scientific International) to enable microscopic counting. Of the four fractions obtained by this method, over 99% of the stool bacteria could be recovered within the bacterial fraction.

A portion of the dried bacterial mass from each stool sample was pooled to provide a representative sample of faecal bacteria for both the healthy controls and patients with cystic fibrosis. The energy per gram of stool bacteria for each of the pooled samples was determined by bomb calorimetry in an attempt to estimate the proportion of stool energy that may be attributed to stool bacteria.

Values are presented as mean (SEM). Statistical comparisons between the patients with cystic fibrosis and control subjects were performed using the Student's t test and differences between means were considered significant where $p<0{\cdot}05$. Associations between variables were tested by the Pearson product moment correlation coefficient (R).

Results

The gross energy intakes and stool energy losses are shown in the table for both healthy controls and patients with cystic fibrosis. There was no significant difference in gross energy intakes for both the healthy control subjects and the patients with cystic fibrosis (9·46 (0·29) compared with 9·93 (0·79) MJ/day; this was not significant). In healthy control children stool energy averaged 0·34 (0·03) MJ/day, 3·5% of the gross energy intake (range 1·3–5·8%; fig 1). In contrast, the stool energy losses were three times greater in patients with cystic fibrosis than controls (0·99 (0·09) MJ/day; $p<0{\cdot}0001$), 10·6% of the gross energy intake (range 4·9–19·7%; $p<0{\cdot}0001$). In patients with cystic fibrosis, dry stool weight and wet stool weight were approximately twice as great as the controls (37·9 (3·6) compared with 16·8 (1·8) g; $p<0{\cdot}0001$ and 120·8 (9·8) compared with 69·3 (8·2) g; $p<0{\cdot}001$).

The amount of lipid within the stool of healthy control children averaged 2·2 (0·2) g/day, 2·9% of the lipid intake (range 1·3–4·4%; fig 2). In patients with cystic fibrosis stool lipids were four times greater than in the controls (9·9 (1·2) g/day; $p<0{\cdot}0001$), equivalent to 14·6% of the lipids intake (range 2·8–37·9%; $p<0{\cdot}0001$). Nitrogen in the stool of healthy control children averaged 1·1 (0·1) g/day, 10·8% of nitrogen intake (range 4·9–19·1%; fig 2). In patients with cystic fibrosis stool nitrogen was twice as great as the controls (2·5 (0·5) g/day; $p<0{\cdot}01$), equivalent to 22·5% of nitrogen intake (range 4·0–59·9%; $p<0{\cdot}01$).

There were weak associations between stool lipid and stool energy with only 26% and 19% of the variance in stool energy attributable to differences in stool lipid for both the control subjects and patients with cystic fibrosis respectively ($R=0{\cdot}51$ and $R=0{\cdot}43$; fig 3). Stool lipid accounted for significantly more of the stool energy in the patients with cystic fibrosis (41%) than healthy controls (29%; $p<0{\cdot}05$).

While stool lipid was a poor predictor of stool energy, a closer association could be demonstrated between stool energy and either the wet weight or the dry weight of the stool in both the control subjects ($R=0{\cdot}77$, $R=0{\cdot}98$ respectively; fig 4 and 5) and patients with cystic fibrosis ($R=0{\cdot}86$, $R=0{\cdot}98$ respectively). Approximately 59% and 74% of the variance in stool energy could be attributed to differences in wet stool weight in the control and cystic fibrosis patients respectively. For both groups, 96% of the variance in stool energy could be attributed to differences in dry stool weight.

The regression lines describing the association between the energy content and the dry weight of stool were similar for the control subjects and the patients with cystic fibrosis. For

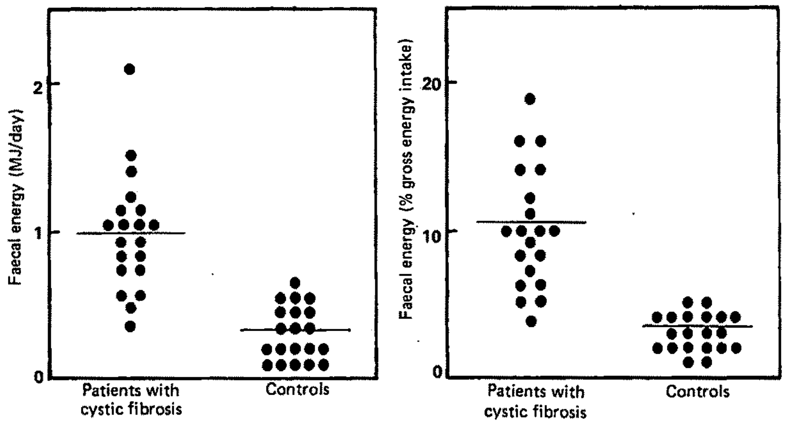

Figure 1 Daily stool energy losses expressed as MJ/day and as a % of the gross energy intake for each of the control subjects and cystic fibrosis patients. The bars represent the mean values.

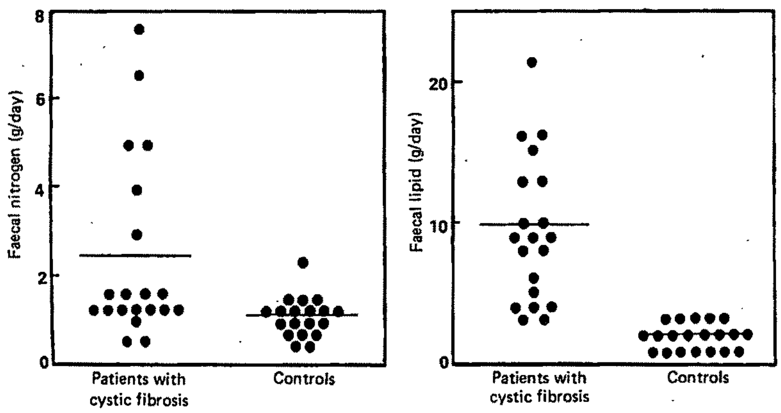

Figure 2 Daily stool lipid and nitrogen losses (g/day) for each of the control subjects and cystic fibrosis patients. The bars represent the mean values.

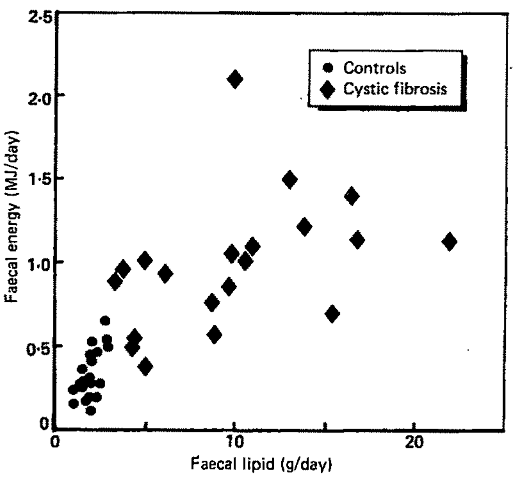

Figure 3 Stool energy versus stool lipid losses for the control subjects and cystic fibrosis patients.

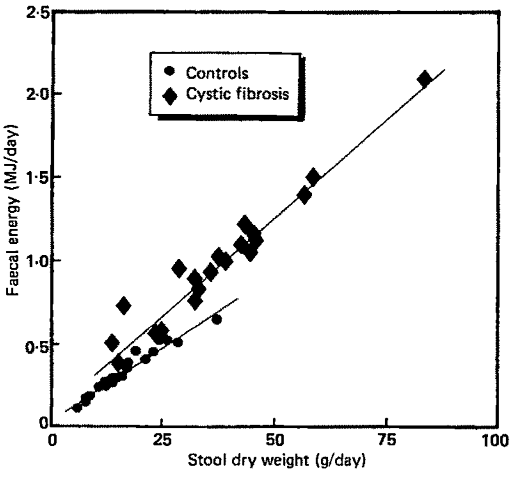

Figure 4 Stool energy losses versus stool dry weights for the control subjects and the cystic fibrosis patients.

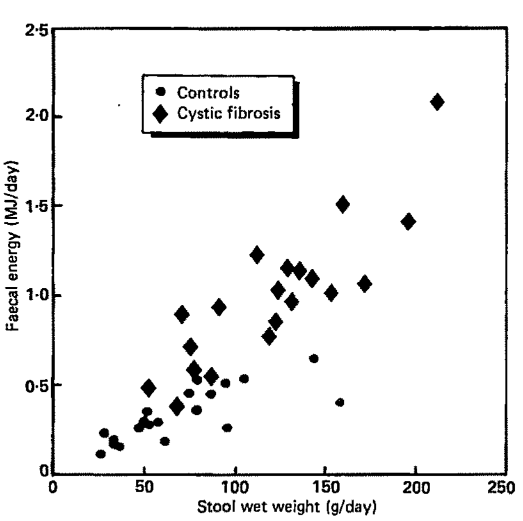

Figure 5 Stool energy losses versus stool wet weights for the control subjects and the cystic fibrosis patients.

the control subjects the regression equation describing the relationship between stool energy and dry stool weight was: stool energy (kJ/day)=35·5+(stool dry weight (g/day)×18·0); the standard error of the estimate (SEE) was 30·6. The regression equation for the patients with cystic fibrosis was: stool energy (kJ/day) =78·9+(stool dry weight (g/day)×24·0); SEE=91·4. Attempts to determine whether the two lines were similar or represented two independent associations using methodology described by Zerbe *et al*[15] showed that the two lines were not statistically different. As it was not possible to differentiate between the two lines, a single expression to describe the association between stool energy and stool dry weight for both subject groups was determined; stool energy (kJ/day)=−55·7+(stool dry weight× 26·1), SEE=96·0, R^2=95·3%). Stool energy per gram of dry weight of stool was significantly greater in the patients with cystic fibrosis compared with the control subjects (27·0 (0·7) kJ/g compared with 20·4 (0·4) kJ/g; p<0·0001).

More obvious differences between controls and cystic fibrosis patients were observed for the association between the energy and the wet weight of stool (controls: stool energy (kJ/day)=123·0+(stool wet weight (g/day)×3·1), SEE=95·3; patients with cystic fibrosis: stool energy (kJ/day)=68·9+(stool wet weight (g/day)×7·6), SEE=202·0). Stool energy per gram of wet weight of stool was significantly greater in the patients with cystic fibrosis compared with control subjects (8·0 (0·4) kJ/g compared with 5·5 (0·3) kJ/g; p<0·0001).

In healthy controls, stool bacterial mass averaged (SEM) 4·3 (0·4) g/day and was equivalent to 27% of the stool dry weight (range 17–42%). In patients with cystic fibrosis, stool bacterial mass was three times greater (13·4 (2·1 g/d; p<0·001) and was equivalent to 35% of stool dry weight (range 19–61%, p<0·01). Determination of the energy content of the pooled stool bacterial mass samples showed an energy content per gram of bacterial mass of 20·4 kJ/g and 23·8 kJ/g for the pooled sample from healthy controls and patients with cystic fibrosis respectively. Using these values, the energy content of the bacteria in each of the subjects was estimated. Despite the difference in the energy content of the stool between the controls subjects and cystic fibrosis patients, a similar percentage of the energy in the stool could be attributed to the bacteria (27·0 (1·6)% and 30·8 (2·8)%; this was not significant).

Discussion

The aim of the present study was to determine the magnitude and origins of stool energy losses in healthy children and in patients with cystic fibrosis on their habitual pancreatic enzyme replacement treatment. To our knowledge, this represents the first description of stool energy losses in these subject groups. In healthy children even though the energy within the stool may be relatively small, these modest losses of energy may be important as imbalances in the availability of energy from the diet may be sufficient to limit growth. In diseased states such as cystic fibrosis, where there is the maldigestion and malabsorption of lipid, protein, and carbohydrate, stool energy losses may be substantially increased. Thus if these losses in stool energy are left uncorrected, it is even more likely that growth may be restricted.

Three major components are believed to contribute to the energy within the stool: maldigested and malabsorbed dietary residue, endogenous secretions and cellular debris (for example, intestinal glycoproteins and mucopolysaccharides), and the colonic bacterial microflora.[16 17] While the relative proportions of each component may vary with dietary intake, the extent of maldigestion and malabsorption and mucus production in the gut, the relative contribution made by each of these components to stool energy losses in health and disease remains unclear. Similarly, the relative proportions of energy within the stool derived from lipid, protein, and carbohydrate have not been previously described.

Much of our understanding of stool energy, lipid, and protein losses of healthy children aged 5–16 years is derived from studies in adult subjects where stool energy was normally less than 1·0 MJ/day and equivalent to 5% of gross energy intake.[1] In the present study, stool energy losses in a group of normal healthy children averaged 337 kJ/day or 3·5% of gross energy intake. The amount of lipid and nitrogen within the stool in normal adults has been previously reported to be less than 5 g/day and 2 g/day respectively in normal adults.[18] In the present study, stool lipid and nitrogen in this group of normal healthy children were on average 2·2 g/day and 1·1 g/day respectively. These results for stool lipid and nitrogen are comparable with those reported in children by other workers.[19]

In contrast to the results for the normal healthy children, it would appear that in the group of cystic fibrosis patients on pancreatic enzyme replacement therapy who believed themselves to be comparatively asymptomatic, stool energy losses were substantially greater and were equivalent to between 5–20% of the gross energy intake. This would suggest that raised stool energy losses may continue to contribute in part towards an energy deficit that may be sufficient to limit growth or cause weight loss. We have not attempted to measure the efficacy of pancreatic enzyme replacement, although it is clear that in some of the patients with cystic fibrosis the replacement regimen may be inappropriately regulated by self titration in the absence of gastrointestinal symptoms. As the heterogeneity of the physical abnormalities of cystic fibrosis may be related to a specific gene mutation, it has been suggested that the differences in resting energy expenditure in cystic fibrosis may be associated with a defective gene product (A O'Rawe *et al*, personal communication). In the light of this observation, it is interesting to speculate whether the genetic nature of the disease may account for the increased stool energy losses within the present group of cystic fibrosis patients.

Although previous studies examining the efficacy of enzyme replacement have noted that stool lipid losses in patients with cystic fibrosis were approximately 12–15 g/day[3 4] with nitrogen losses of approximately 1–2 g/day when using pancreatic enzyme replacement therapy,[20] no information on stool energy losses is available. As the stool lipid and nitogren losses in patients with cystic fibrosis in the present study were comparable with these values from earlier investigations, this would suggest that the pancreatic enzyme replacement therapy in the cystic fibrosis patients in this study reduced stool lipid and nitrogen to similar degrees. Despite this reduction in stool lipid and nitrogen, from the present study it appears that stool energy could still be equivalent to up to 20% of the gross energy intake in cystic fibrosis patients on their habitual enzyme replacement treatment.

It is also apparent that stool energy losses can not be simply related to lipid losses. While it is commonly assumed that a reduction in stool lipid losses would also represent a small amount of energy lost within the stool, it appears that cystic fibrosis patients with small lipid losses within the stool may have high stool energy losses. This would also imply that a reconsideration of the present approach to address the efficacy of pancreatic enzyme replacement by the measurement of steatorrhoea may be required.

We would suggest that the routine measurement of stool energy may provide a more accurate assessment of the extent to which pancreatic enzyme replacement treatment normalises stool energy loss in patients with cystic fibrosis. However, the facilities required to measure directly the stool energy are not generally available in clinical practice. As the regression line expressing the association between the energy present within the stool and the wet weight of the stool passes close to the origin, the use of a simple ratio based upon the slope of the line would be justified. From the data available in this study, it would appear that 8 kJ of energy is present in each gram of wet stool. With this information, an estimate of the extent of energy losses in the stool may be derived by simply determining the weight of stool passed each day. In the present group of cystic fibrosis patients, the 95% confidence intervals for the error in predicting stool energy loss from the wet weight of stool using a value of 8 kJ/g stool wet weight ranged from −12 to 6% (mean −3%). This method may provide a more reliable means of evaluating the extent of maldigestion and malabsorption in patients with cystic fibrosis than the measurement of stool lipid. The apparent constancy of the energy per dry weight of stool in both the control subjects and the cystic fibrosis patients would imply that the composition of stool must remain relatively similar between individuals despite a wide range in stool energy losses.

It is generally assumed that all of the energy within the stool may be attributable to maldigested and malabsorbed dietary residue in cystic fibrosis. Stool energy losses could also be derived from endogenous secretions and cellular debris as well as the colonic bacterial microflora. Although it has not been possible to quantify directly mucus and epithelial cells losses within the faeces, this component may form a substantial part of stool energy losses in cystic fibrosis where mucus production is raised. It is comparatively simple to measure the amount of bacteria within human faeces using a novel technique described by Stephen and Cummings.[14] In the present study this method has enabled the measurement of the relative contribution made by the bacteria to total energy lost within the stool in both normal healthy children and cystic fibrosis patients. To our knowledge there have been no other studies which have demonstrated the contribution made by the bacteria to the total energy lost within the stool.

Stephen and Cummings have shown that the bacterial microflora represented 55% of the total dry weight of stool in healthy male adults.[14] In the present study, approximately 27% and 34% of the stool dry weight were attributable to the bacterial microflora in both the normal healthy children and patients with cystic fibrosis respectively. It appears that the bacterial microflora could account for approximately 30% of total stool energy losses in both the cystic fibrosis patients and normal healthy children. This study represents the first description of the proportion of energy within the stool which can be attributed to the bacteria. It is clear that a major component of the stool is not simply maldigested and malabsorbed dietary residue but that part of the energy within the stool may be attributable to the bacterial microflora.

In conclusion, the present study has measured stool energy losses in a group of normal healthy children and patients with cystic fibrosis. The raised stool energy losses in the patients with cystic fibrosis with their habitual enzyme replacement therapy may contribute towards an energy deficit that may be sufficient to limit growth. We have shown that stool energy may be predicted from the wet or dry weight of stool. Estimating the energy within the stool each day from stool wet weight may provide a simple way of evaluating the extent to which maldigestion and malabsorption in patients with cystic fibrosis may be improved by pancreatic enzyme replacement therapy. It should not be assumed that all of this stool energy in the control subjects and cystic fibrosis patients is simply maldigested and malabsorbed dietary residue. It appears that the bacterial microflora may be a major component of the energy within the stool in both healthy children and patients with cystic fibrosis.

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Pylorus 6 balloonists 0

If balloon dilatation can be used so successfully in the heart and blood vessels and, indeed, in almost any tubular structure, why not in pyloric stenosis? Canadian workers recently tried it and unfortunately scored six own goals.

A report from Halifax, Nova Scotia (Hayashi *et al*, *Journal of Pediatric Surgery* 1990;25:1119–21) describes the use of a balloon in six babies with hypertrophic pyloric stenosis. In order to check on the safety of the procedure it was done with direct observation of the pylorus at operation. After a right upper quadrant transverse incision the balloon was passed through the mouth and its position in the pylorus was checked by the surgeon before it was inflated.

A perforation of the mucosa occurred in one baby and in the others the split in the pyloric muscle was deemed inadequate. In three there was no split, in two it was partial, and the only child with a complete split was the one with the perforation.

Hard luck! It looks as if Ramstedt's operation will have to stay, at least for the time being.

ARCHIVIST

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Urinary oxalate and glycolate excretion and plasma oxalate concentration

T M Barratt, G P Kasidas, I Murdoch, G A Rose

Abstract

The diagnosis of primary hyperoxaluria in young children is hampered by the lack of a reliable reference range for urinary oxalate excretion, especially in infants. We present data on urinary oxalate and glycolate excretion in 137 normal children, on the plasma oxalate concentration in 33 normal children and 53 with chronic renal failure, and on amniotic fluid oxalate concentration in 63 uncomplicated pregnancies. The urinary oxalate:creatinine molar ratios were log normally distributed: mean (range) values were <1 year 0·061 (0·015–0·26), 1–5 years 0·036 (0·011–0·12), 5–12 years 0·030 (0·0059–0·15), and >12 years 0·013 (0·0021–0·083). Geometric mean (range) plasma oxalate concentration in the normal children was 1·53 (0·78–3·02) μmol/l and was independent of age. The mean (SD) plasma oxalate:creatinine molar ratio in these normal children and 50 with chronic renal failure was 0·033 (0·013), and was independent of age and renal function. Mean (SD) amniotic fluid oxalate concentration was 19·0 (4·3) μmol/l.

Primary hyperoxaluria type 1 is an inborn error of glyoxalate metabolism characterised by excessive production and urinary excretion of oxalate and glycolate.[1] Two thirds of the cases present before the age of 5 years with calcium oxalate urolithiasis, and the disease usually runs a progressive course leading to end stage renal failure with systemic oxalosis before adulthood. It is important to diagnose the condition at an early stage so that therapeutic measures can be implemented to reduce the severity of the disease by modifying the risk factors associated with the deposition of calcium oxalate in the urinary tract and in the tissues.

There is, however, a paucity of information in the literature on the urinary excretion rates and plasma concentrations of oxalate and glycolate in young normal children. The report by Gibbs and Watts gives values for urinary oxalate excretion in a few normal children, the youngest of whom was 2·5 years of age,[2] and the preliminary report of Kasidas and Rose presented only limited data on children under 1 year of age.[3]

Without reliable reference ranges the interpretation of urinary oxalate concentrations in young children has been uncertain. There is also some doubt about the appropriate correction of oxalate excretion for body size, and in any case the collection of accurately timed urine specimens from young children is notoriously difficult. In some cases a urine sample is unobtainable because of anuric renal failure: in these circumstances the association between the plasma concentrations of oxalate and creatinine has been used to support the diagnosis of primary hyperoxaluria, but again reference ranges are lacking. Finally, we considered the possibility of prenatal diagnosis of the disorder from amniotic fluid oxalate concentration, but good normal data were not available.

To address these problems we measured: (i) urinary oxalate:creatinine and (ii) glycolate:creatinine molar ratios in 137 'normal' children; (iii) plasma oxalate and creatinine concentrations in 33 'normal' children and 53 children with renal damage; and (iv) amniotic fluid oxalate concentration from 63 uncomplicated pregnancies.

Patients and methods

The group of 137 'normal' children were aged 0·1 to 17·0 years, and consisted of patients admitted to the Hospital for Sick Children, Great Ormond Street, London, for minor surgery unrelated to the urinary or gastrointestinal tract, their siblings, and the children of the staff and their friends. The height and weight were known in 92 of them. The urine sample obtained was the second in the morning—that is, the first sample passed after the overnight urine had been voided. Plasma was obtained from 33 of the children admitted for minor surgery who were having blood taken for clinical purposes and from 53 children attending the renal clinic of the hospital with various degrees of renal failure. Samples of amniotic fluid were obtained from 63 pregnant women at 16–18 weeks' gestation undergoing amniocentesis at St George's Hospital, London.

Oxalate concentration was measured enzymatically with immobilised oxalate oxidase,[4] [5] glycolate concentration with glycolate oxidase,[6] and creatinine by Autoanalyser II using a modified Jaffé alkaline picrate reaction. For plasma and amniotic fluids, ultrafiltrates were prepared for analysis using Amicon Centriflo ultrafiltration membrane cones with molecular weight cut off of 25 000 daltons.

Some of the data were log normally distributed: means, ranges, and correlations were therefore calculated on log transformed results. Surface area was calculated from the formula of Dubois and Dubois.[7]

Results

(i) URINE OXALATE:CREATININE MOLAR RATIO

The urine oxalate:creatinine molar ratio (UOx:

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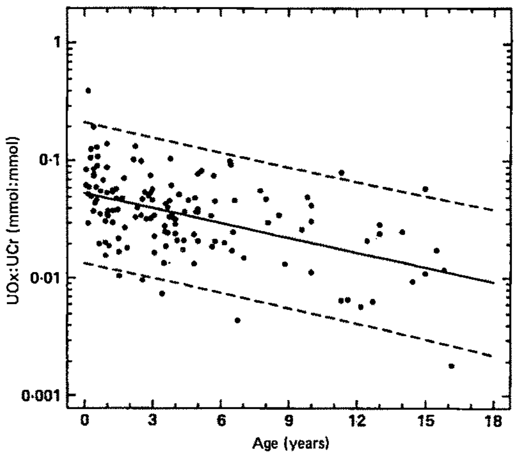

Figure 1 Urinary oxalate:creatinine molar ratio (UOx:UCr) compared with age: the regression equation is log (UOx:UCr)=−1·27−0·0425×age (years) (r=−0·50; p<0·0001).

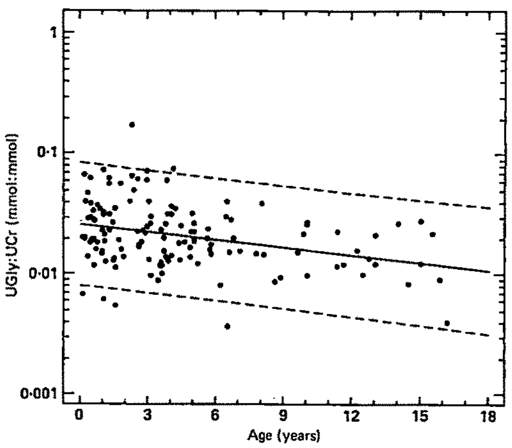

Figure 2 Urinary glycolate:creatinine molar ratio (UGly:UCr) compared with age: the regression equation is log (UGly:UCr)=−1·60−0·0223×age (years) (r=−0·32; p<0·0001).

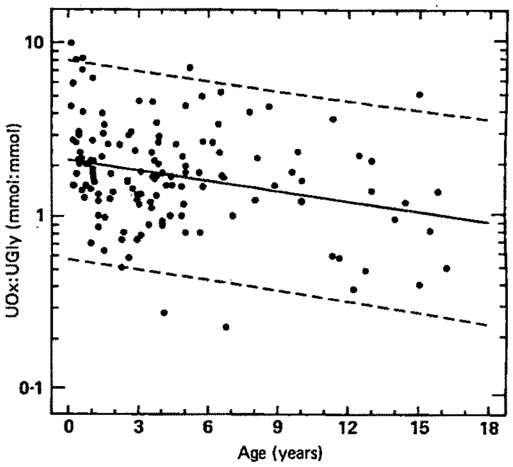

Figure 3 Urinary oxalate:glycolate molar ratio (UOx:UGly) compared with age: the regression equation is log (UOx:UGly)=−0·323−0·0200×age (years) (r=−0·27; p<0·005).

UCr) decreased with age ($r=-0{\cdot}50$, $p<0{\cdot}0001$) (fig 1). The regression equation was:

$$\log(\mathrm{UOx:UCr})=-1{\cdot}27-0{\cdot}0425\times\mathrm{age\ (years)}$$

Mean and ranges calculated on log transformed data are given in the table. UOx:UCr was significantly higher in infants than in older children ($p<0{\cdot}001$). In the 92 children for whom height and weight were known, log (UOx:UCr) correlated similarly with age ($r=-0{\cdot}50$), weight ($r=-0{\cdot}50$), and surface area ($r=-0{\cdot}48$), better than with height ($r=-0{\cdot}40$), but the correlation coefficients were not significantly different from each other.

(ii) URINE GLYCOLATE:CREATININE MOLAR RATIO

The urine glycolate:creatinine ratio (UGly:UCr) also declined with age ($r=-0{\cdot}32$, $p<0{\cdot}0005$) (fig 2):

$$\log(\mathrm{UGly:UCr})=-1{\cdot}60-0{\cdot}0223\times\mathrm{age\ (years)}$$

The decline in UGly:UCr with age was less than that of UOx:UCr, and as a consequence, UOx:UGly also declined with age ($r=-0{\cdot}27$, $p<0{\cdot}005$) (fig 3):

$$\log(\mathrm{UOx:UGly})=-0{\cdot}323-0{\cdot}0200\times\mathrm{age\ (years)}$$

(iii) PLASMA OXALATE AND CREATININE CONCENTRATIONS

In the healthy children the plasma oxalate (POx) concentration was independent of age ($r=0{\cdot}09$, $p>0{\cdot}1$) or plasma creatinine concentration (PCr). Geometric mean (range) POx was 1·53 (0·78–3·02) µmol/l. When the children with renal disease were included there was a highly significant correlation between POx and PCr, which were both log normally distributed ($r=0{\cdot}93$, $p<0{\cdot}0001$) (fig 4). The regression equation was:

$$\log \mathrm{POx}=-1{\cdot}39+0{\cdot}94\times\log \mathrm{PCr}$$

This association gives POx=1·6 µmol/l when PCr=50 µmol/l, and POx=14·4 µmol/l when PCr=500 µmol/l. The mean (SD) POx:PCr ratio was 0·033 (0·013), was independent of age, and never exceeded 0·07.

(iv) AMNIOTIC FLUID OXALATE CONCENTRATION

Amniotic fluid oxalate concentration was approximately normally distributed with a mean (SD) of 19·0 (4·3) µmol/l.

Urinary oxalate and glycolate excretion

	<1 year (n=27)	*1–<5 years (n=67)*	*5–<12 years (n=31)*	*>12 years (n=12)*
UOx:UCr (mmol:mmol)	0·061 (0·015–0·26)	0·036 0·011–0·12)	0·030 (0·0059–0·15)	0·013 (0·0021–0·083)
UGly:UCr (mmol:mmol)	0·024 (0·0079–0·070)	0·023 (0·0057–0·091)	0·016 (0·0057–0·046)	0·013 (0·0040–0·041)
UOx:UGly (mmol:mmol)	2·6 (0·69–9·7)	1·6 0·50–4·9)	1·8 (0·41–8·1)	1·0 (0·21–5·1)

Mean (range) calculated on logged data.

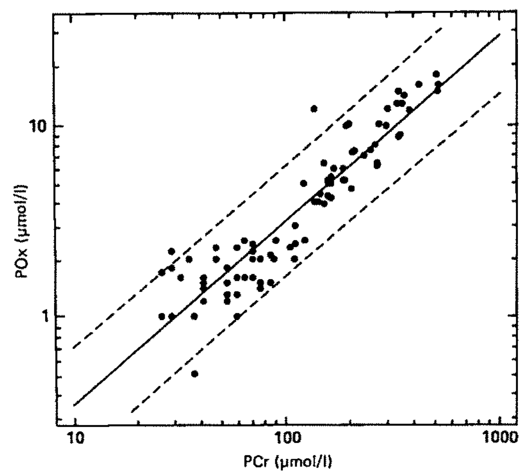

Figure 4 Plasma oxalate (POx) and creatinine (PCr) concentrations: in the 'normal' children mean (SD) POx was 1·65 (0·46) μmol/l. Including the children with chronic renal failure the regression equation was: $\log POx = -1{\cdot}39 + 0{\cdot}94 \times \log PCr$ *(*$r = 0{\cdot}93$*;* $p < 0{\cdot}0001$*).*

Discussion

The reference ranges presented facilitate the diagnosis of hyperoxaluric states. UOx:UCr is significantly higher in infants than in older children, clearly an important consideration in the evaluation of oxalate excretion in young children. Barratt *et al* argued that an inverse correlation of UOx:UCr with height was to be expected as oxalate excretion is proportional to body surface area (and thus to the square of height) whereas creatinine excretion is proportional to weight (and thus to the cube of height).[8] Although there was a clear association between UOx:UCr and body size, a specific association with height was not observed. Also, UOx:UCr will also be influenced by factors independently affecting creatinine excretion—for example, reduced muscle bulk in malabsorption may result in low rates of creatinine excretion and thus spuriously high values for UOx:UCr.

UGly:UCr also declines with age, but less steeply than UOx:UCr, and UOx:UGly is higher in infants than in younger children. The same phenomenon is evident in primary hyperoxaluria[8]; the reason is unknown, but it does suggest a greater risk of oxalate deposition in young children with disorders of oxalate metabolism. A raised value of UOx:UCr with a normal value of UGly:UCr suggests enteric rather than primary hyperoxaluria.

Geometric mean POx was, at 1·53 μmol/l, slightly lower but not significantly lower than adult values of 2·03 (0·52) μmol/l.[5] It was independent of age, but rose in proportion to PCr in chronic renal failure in children as in adults. POx:PCr averaged 0·033, and never exceeded 0·07[9]; values greater than this in patients with renal failure suggest the possibility of primary hyperoxaluria.

Rose *et al* reported a case where the prenatal diagnosis of primary hyperoxaluria was confirmed after the finding of a raised oxalate concentration of 110 μmol/l in the amniotic fluid.[10] However, Leumann *et al* reported another case where primary hyperoxaluria was subsequently confirmed despite a normal level of oxalate in the amniotic fluid.[11] With the elucidation of the primary enzyme defect,[12] antenatal diagnosis by fetal liver biopsy has now become possible for type 1 primary hyperoxaluria.[13] However, this is a highly specialised procedure not always available and does not detect type 2 hyperoxaluria. Hence there may still be a role for the measurement of amniotic fluid oxalate concentration, which needs to be further evaluated.

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Major problems with paediatric bed usage statistics?

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Abstract

This study was carried out on the way in which children's beds were used by the specialty of paediatrics in a district general hospital. Five differing ways were found of interpreting the present Department of Health guidelines on health services information (Körner recommendations). These gave *bed occupancy* figures varying between 73% and 106%; *throughput figures* varying between 23·8 and 34·7 discharges per bed; and *turnover interval* varying between −0·17 and 1·1 days for the same group of paediatric admissions. For comparisons of efficiency and costs between hospitals, which are based upon bed utilisation statistics, it is essential that there is standardisation of method of analysis.

Analysis of bed usage is increasingly being used to assess the efficiency of use of resources. Comparison between districts may be used by managers to identify inefficiency or alternatively, overpressed services. There are particular constraints applying to the admissions of children: that is, children under 16 should not be admitted to adult wards and a high proportion of admissions into paediatric medical care and general surgical and orthopaedic care are acute and thereby uncontrolled. Children's beds tend to be used by a number of specialties treating children, including paediatric medicine. There needs to be a percentage occupancy of children's beds that is low enough to cater for peak usage (to avoid inability to admit an acutely ill child or the need to 'sleep out' the child on an inappropriate ward) and yet high enough to permit optimal use of resources.

In 1984, a Department of Health and Social Security (DHSS) health building note states 'Para 1·13: The provision and use of beds for children vary widely among health authorities. The latest regional figures available suggest a range from 0·6 to 1·4 occupied beds per 1000 population under age 1, with only three regions having more than 1·0 per 1000. With current clinical practice, it is considered that an occupancy rate of 75% is the optimum to allow for flexibility in acute cases. This would indicate provision of between 0·9 and 1·1 beds per 1000 population under age 16, excluding mentally handicapped children and special care baby cots.'[1] (Also excluded from this figure would appear to be those children with infectious disease.) Before attempting therefore to identify what an ideal occupancy might be, it is important to ensure that analysis of bed usage is standardised within a district and preferably between districts so that useful comparisons may be made. This study has been conducted to determine whether this analysis is practical in a district general hospital children's unit, taking note of the new ways of analysing bed usage recommended by the Körner report.[2]

Methods

(A) WARD CHARACTERISTICS (TABLES 1 AND 2)

The two wards studied were A and B wards at Pinderfields Hospital.

(i) A ward has 20 beds and nominally caters for children being admitted under the general and urological surgeons and orthopaedic surgeons. Because of the nature of the accommodation, however, children admitted as paediatric medical cases aged over 10 years are preferably admitted there also. Additionally

Table 1 Bed usage at Pinderfields Hospital over a nine month period. Numbers are bed days/month

A ward (nominally 11 surgical, 2 urology, 7 orthopaedic beds)	*June 1989*	*May 1989*	*April 1989*	*March 1989*	*February 1989*	*January 1989*	*December 1988*	*November 1988*	*October 1988*
Paediatric	92	92	98	121	69	75	155	110	137
Non-paediatric	179	238	242	238	300	220	188	204	200
Total No occupied bed days	2958								
Total No available bed days	5460								
Bed occupancy	54%								
No of paediatric bed days	949	(32% occupied bed days, 17% available bed days)							
No of non-paediatric bed days	200	(68% occupied bed days, 37% available bed days)							

B ward (nominally 19 paediatric beds)	*June 1989*	*May 1989*	*April 1989*	*March 1989*	*February 1989*	*January 1989*	*December 1988*	*November 1988*	*October 1988*
Paediatric	311	313	356	330	328	372	360	355	349
Non-paediatric	55	84	35	24	12	35	84	88	103
Total No occupied bed days	3594								
Total No available bed days	5187								
Bed occupancy	69%								
No of paediatric bed days	3074	(85% occupied bed days, 59% available bed days)							
No of non-paediatric bed days	520	(15% occupied bed days, 10% available bed days)							

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Table 2 Bed usage in A ward

Speciality	*June 1989*	*May 1989*	*April 1989*	*March 1989*	*February 1989*	*January 1989*	*December 1988*	*November 1988*	*October 1988*
Dermatology	16	—	9	—	13	2	13	11	11
General medicine	8	2	—	—	1	5	—	—	—
Neurology	—	—	—	—	1	—	—	—	—
Neurosurgery	11	12	23	31	17	13	8	34	30
Orthopaedics	96	148	153	159	180	116	123	89	76
Paediatrics	92	92	98	121	69	75	155	110	137
Plastic surgery	—	1	—	2	1	1	—	1	—
General surgery	41	69	50	40	73	80	38	69	82
Urology	7	6	5	3	14	3	6	—	—
Oral	—	—	2	—	—	—	—	—	1
Ophthalmology	—	—	—	3	—	—	—	—	—
Total	271	330	340	359	369	295	343	314	337

Total No occupied bed days=2958, total No available bed days=5460, bed occupancy=54%.
No of orthopaedic bed days=1140 (38% occupied bed days, 20% available bed days); No of paediatric bed days=949 (32% occupied bed days, 17% available bed days); No of general surgery bed days=542 (18% occupied bed days, 10% available bed days).

there are two cubicles on A ward and occasionally small babies are admitted under the care of the paediatricians there.

(ii) B ward has 19 beds with eight mother and baby cubicles. The majority of the admissions are paediatric medical with some occasional general surgical admissions.

(iii) Children admitted under the care of the neurosurgeons are also admitted onto A or B ward according to their age: with their longer duration of stay, they produce a significant workload and bed occupancy onto these wards. However, there is no planned allocation of beds for their use.

(B) SPECIALTY BED ALLOCATION

The Körner report made recommendations that included the need to identify the *number of beds* intended to be used by each specialty and, additionally, to describe how each *ward* was intended to be used.[2] This would then allow analysis, by specialty and ward, of the actual bed use compared with what was intended. Particular emphasis in the recommendations was given to analysis of length of stay and throughput per available bed. Throughput was to be calculated '. . . in terms of the number of beds that the specialty was intended to use rather than the beds estimated to be available'. Subsequently the analysis of turnover interval for each specialty was given emphasis.

Both before the Körner recommendations and since their implementation it has been necessary to determine a way of allocating empty beds to specialties. In Yorkshire Regional Health Authority a modified SH3 return has been introduced that identifies for each specialty the available bed days, occupied bed days, and 'finished hospital stays'—a term that encompasses discharges, deaths, and transfers to other hospitals. Bed availability for wards open overnight is to be measured at midnight. There is a need to adapt the number of intended available bed days to allow for unscheduled additional beds or bed borrowing by other specialties to reflect their actual usage.

Bed occupancy is calculated as follows:

$$\text{Bed occupancy}=\frac{\text{Beds occupied}}{\text{Beds available}}\times 100$$

Variation will occur in the numerator depending upon when in the 24 hour period it was counted, and in the denominator depending upon whether beds were borrowed from or, alternatively, by, the specialty being analysed.

Under the recommendations of Körner, the specialty allocation of beds should be agreed upon by management within a district as well as identifying the wards in which those beds are placed.

The official way adopted in Wakefield at present for allocating the children's beds on A and B wards in this hospital is: B ward, 19 paediatric beds and A ward, 20 surgical beds.

(C) STATISTICAL ANALYSIS OF BED USAGE

The following computer systems were used in the analysis of bed usage.

(i) Patient administration system (PAS)

PAS was developed by inter-regional collaboration comprising six regional health authorities and the computer company ICL and run on an ICL mainframe. It is a district wide system that keeps track of a patient through his or her stay in hospitals within the district, and produces statistical reports required by the health authority. On PAS additional reports are available that show the number of patients on each ward at midnight on each day during the month by specialty.

(ii) SH3

The reference name given to the hospital statistics return in pre-Körner days, it records activity about each specialty in each hospital—that is, number of allocated beds, average number of available beds, discharges per available bed, etc.

(iii) YSH3 B

A manual return to the Yorkshire Regional Health Authority for each hospital site that shows available beds, bed usage, and finished hospital stays.

(iv) ASTRAC

Advisor information system (AIS) runs on an IBM 9370 using IBM application software (AS).

Extracts of data are taken from the district information system (DIS)—which originates from PAS—to produce standard reports not accessible to the PAS and DIS systems. One of these reports shows bed occupancy by specialty by ward per day. This is different to the SH3 report in that it records all bed episodes which started, ended, or were current during the 24 hour period.

(D) BED USAGE PROBLEMS

The problem that appeared to be present was that the 19 beds on B ward that were identified as available for paediatrics were not always suitable for a child who was admitted: for example, a 12 year old girl with asthma would be admitted onto A ward, thereby borrowing a bed from a surgical specialty, while leaving several beds unused but 'available' for paediatrics on B ward. Hence the calculation of throughput per bed (or occupancy) for that period would be based upon: the number used +1 and the number available +1. Thus if there had been 12 patients on B ward before the girl was admitted, the occupancy for paediatrics was 12/19 (63%) but when she was admitted onto A ward would be 13/20 (65%). If, however, an alternative system were used of allocating 19 beds for the paediatric specialty between the 39 children's beds (19 on B ward and 20 on A ward) then the occupancy would be 13/19 (68%). The calculation of throughput (discharges per available bed) would similarly be affected in an adverse way for the specialty by being based upon 20 rather than 19 beds. In order therefore to examine this problem a variety of differing ways of analysing the use of beds was identified.

Results (see table 3)

OPTION 1

The SH3 return equals the number of beds on B ward (n=19) multiplied by the number of days in the quarter, to obtain bed availability. This does not take into account bed borrowing either by surgical specialties of the beds on B ward or by paediatrics of the children's surgical beds on A ward. (The data returned over the period of the study upon which health service indicators are based are from option 1.)

Table 3 Examples of how different bed availability figures can alter performance indicators in paediatrics

	Bed occupancy (%)	*Throughput*	*Turnover interval*
Quarter ending December 1988:			
Option 1	89	27·84	0·37
Option 2	80	25·09	0·75
Option 3	91	28·35	0·31
Option 4	84	26·15	0·59
Option 5	106	33·10	−0·17
Quarter ending March 1989:			
Option 1	80	26·26	0·73
Option 2	73	23·83	1·10
Option 3	91	30·02	0·27
Option 4	76	24·97	0·91
Option 5	106	34·68	−0·16
Quarter ending June 1989:			
Option 1	75	25·84	0·93
Option 2	74	25·67	0·96
Option 3	87	29·81	0·44
Option 4	79	27·07	0·76
Option 5	103	35·43	−0·08

OPTION 2

This takes into account bed borrowing—that is, beds borrowed from B ward by other specialties and unavailable to paediatrics and beds borrowed by paediatrics from A ward and the intensive care unit and others and available to paediatrics. It should be noted that:

(1) From October 1988 to June 1989 beds borrowed by other specialties on B ward (see tables 1 and 2), and therefore unavailable to paediatrics, equalled 777. (Because this figure is taken from ASTRAC it is inflated as ASTRAC counts any occupancy of a bed during the day whereas PAS only counts those occupied at 12 midnight and identified only 520 of these 777 bed days.)

Beds borrowed by paediatrics from A ward and therefore available to paediatrics equalled 949 (figure obtained using PAS). Beds in the intensive care unit and other beds also available to paediatrics equalled 201.

(2) The figure borrowed by paediatrics (from other wards and the intensive care unit) was always calculated at 100% occupancy—for example, revised bed days figure for the period October 1988 to June 1989 equalled 5565, but of this number 1155 (20%) were always calculated at 100% occupancy.

OPTION 3

This takes option 2 as starting point for bed availability. However, where a bed is on A ward and available to paediatrics and in option 2 is credited to paediatrics, but could be accommodated on B ward at midnight (that is, using PAS) (because there are empty beds on B ward), this figure has been subtracted from the bed availability figure. However, because the PAS figure has been used (that is, bed was vacant at midnight) it could be that it is not always logistically possible to place the patient on B ward.

OPTION 4

This takes option 2 as a starting point for bed availability and as in option 3 where a bed is on A ward and could be on B ward, this figure has been subtracted. However this can only be done when it is logistically certain to be possible—that is, when the ASTRAC figure for B ward allows it.

OPTION 5

This identifies all 39 children's beds as a total between A and B wards. Of these 39 beds, 19 nominally are allocated to paediatrics, the remainder to the surgical specialties. Borrowing thereby only occurs when paediatric admissions exceed 19 in total whether they are accommodated on A or B ward. This requires a nominal number of beds to be allocated from the 39 to general surgery, orthopaedics, and urology. When they are vacant and thereby unused by the surgical specialty, the usage is analysed according to the nominal allocation to each of those specialties—that is, surgical 11, orthopaedics 7, and urology 2.

Discussion

The results displayed in table 3 indicate how variable the bed occupancy and throughput can be, for the same number of patients with the same length of stay, according to the method used for analysing the bed usage for the specialty of paediatrics. Bed occupancy ranges from 73% to 106% and the throughput ranges from 23·83 to 35·43 discharges per bed/day. A figure of more than 100% occupancy could be derived as more than one patient may occupy a bed in a given day.

Separate analysis of the bed utilisation of the surgical specialties has not at this stage been done. All of the beds identified for the use of paediatrics will be on a children's unit. When children are taken to intensive care, the bed is borrowed. In the surgical specialties, however, only a proportion of the total specialty allocation of beds will be those on the children's ward, but all children treated by those specialties should be on a children's unit.[3–6] Analysis of their utilisation on the children's ward therefore will be diluted by the larger numbers of the surgical specialty beds elsewhere. Nevertheless, it seems desirable to attempt to analyse children's bed usage all together.

For the specialty of paediatrics, analysis of bed utilisation within a district will need to be done using a standardised method which is fair to the specialty. Furthermore, if districts are to be compared with each other and if costs are based upon the way in which beds are used, it is essential that each district adopt the same method of analysing beds. The most reasonable way of allocating beds appears to be option 5 detailed above, and that seems to be more in the spirit of Körner than the other options. The question of how the surgical specialties use of beds within the children's unit would best be analysed has been left unanswered.

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Changes in psychosocial adjustment after renal transplantation

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Abstract

The psychological aspects of transplantation were studied in 29 children and adolescents with functioning renal transplants. Most parents rated their child's physical health as considerably improved after transplantation. They also noted improvements in the child's behaviour and in the quality of family life. When compared with a sample of children being treated by hospital haemodialysis, children who had received transplants had more favourable parental views of behavioural and emotional adjustment, better parental psychiatric adjustment, and indications of superior child rated mood, self concept, and social functioning. Children who had received transplants did, however, show an increase in minor behavioural symptoms compared with healthy controls, and most parents required continuing psychological and social support as well as attention to physical aspects of the child's condition.

Kidney transplantation is associated with improved psychosocial behaviour in children, but there is a continuing need for support for parents in dealing with minor psychological problems after the transplant.

'Most, if not all, paediatric nephrologists caring for infants, children and adolescents with end stage renal disease would advocate successful renal transplantation as the optimal therapeutic modality. This bias is based upon the belief that rehabilitation is significantly superior following successful renal transplantation than that possible with any currently available dialysis modality and that the potential for growth and pubertal development is significantly increased following successful transplantation.'[1]

The success at achieving this ideal varies from region to region and from country to country. Detailed regional statistics are not available but there is information from different countries. In 1987, 5·1 new patients under the age of 15 years per million child population were accepted into end stage renal failure programmes in the United Kingdom.[2] The programme in the North West region of England accepted 8·2/million child population. In 1986 half the children with end stage renal disease in Europe had functioning transplants compared with 60% in this unit.[3] In addition to an overall rise in the number of children being treated the age range has also widened, with increasing numbers of infants and younger children now undergoing successful transplantation. These developments in treatment give rise to a need for a better understanding of the psychosocial changes experienced by this group of children and their parents.

Since the start of transplant programmes for children there have been a number of reports about the social adjustment of children after transplantation. Considerable improvements have been reported in children's health and social functioning after stormy phases immediately after the transplants, and it has been concluded that children with successful transplants have fewer psychosocial difficulties and are better rehabilitated to normal life than those treated by long term dialysis.[4–6] There have, however, been no reports confirming improvements in adjustment by comparing children before and after transplantation. Moreover, in earlier studies children at different stages of treatment (on dialysis and after transplantation) were often studied as one group, thus obscuring differences in psychosocial functioning that could have been attributable to the different stages of treatment.

Some problems that occur after transplantation have been highlighted, including symptoms of depression, poor self esteem, noncompliance with treatment, and preoccupation and concern about the side effects of immunosuppressive medication and poor growth.[7 8] A recent long term outcome study indicated considerable psychological problems, with a quarter of subjects having seen a doctor for a persistent emotional or psychiatric problem in early adulthood.[9] Many authors have noted that ongoing support is necessary to minimise these adverse effects.

Workers in our department have investigated the psychological and social functioning of children at various stages of end stage renal disease and their families.[10 11] Differences in psychosocial adjustment were identified that related to the stage and severity of illness, with a high incidence of difficulties in psychological adjustment among children on hospital haemodialysis, and of minor difficulties in adjustment in schools particularly among a group not yet receiving dialysis. These results highlight the importance of considering or sampling separately subjects at different stages in treatment. Many of the children in our previous study went on to have successful transplant operations. This gave us the opportunity to compare their psychosocial adjustment after transplantation with their adjustment before and during haemodialysis with comparable measures. We were also interested in identifying what psychosocial support, if any, was required by parents after trans-

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plantation in addition to the medical support that was available.

Patients and methods

At the time of the study (1988–9) 29 patients (76%) in the North West regional paediatric end stage renal failure programme had functioning transplants. The rest were on various dialysis treatments, of whom half were awaiting their first renal transplant and half had returned to dialysis after an unsuccessful transplant.

PATIENTS WHO HAD RECEIVED TRANSPLANTS (N=29)

Patients who had received transplants were selected in two stages; in the summer of 1988 parents of all 26 children with transplants that had been functioning between eight and 72 months (mean 31·5 months) who were attending the transplant clinic at Booth Hall Hospital were asked to complete a questionnaire specially designed for this study. This asked about changes in the child's physical and psychological health since the transplant, changes in family life, and about support currently available for the parents. Later in the year and early in 1989 the parents and teachers of the (by then) 29 eligible children were asked to complete questionnaires about the child's psychiatric adjustment. Parents of schoolchildren (n=26) completed the Rutter A behavioural questionnaire, and teachers completed the Rutter scale B. These scales consist of a list of symptoms or items the relative incidence and severity of which during the previous year is rated on a three point scale. The total score is computed and scores of 13 or more (parental scale) and of 9 or more (teachers' scale) indicate that the child has psychological problems and a high risk of psychiatric disorder.[12] Parents of preschool children (n=2) completed the behaviour checklist,[13] and the one school leaver completed the general health questionnaire, which is a measure of adult mental distress or minor psychiatric morbidity.[14] We also asked the parents of each child to give an overall judgment about whether they thought the child had behavioural or emotional problems and to indicate the degree of these difficulties on a three point scale.

Children over 7 years old were asked to complete a questionnaire to assess their depressive symptoms (the Birleson depression inventory[15 16]) and a self esteem questionnaire (the Lipsitt self concept scale[17 18]); we used cut off points of 13 and 30, respectively. Children were also asked to give details about their social lives. Parents were asked whether they had consulted their general practitioners or taken drugs for 'their nerves' during the preceding two years. They also completed the general health questionnaire (GHQ 28).

PATIENTS TREATED BY HOSPITAL HAEMODIALYSIS (N=22)

This group comprised all children attending Booth Hall Hospital between September 1983 and August 1985 for a minimum of six months regular haemodialysis. There were 22 children (16 boys and six girls) with an age range of 3–18 years, mean 13). Seven of the children went on to receive transplants and were included in both the previous group and this one.

PATIENTS NOT BEING TREATED BY DIALYSIS (N=22)

Twenty two children with chronic renal failure attending the paediatric clinic but not receiving dialysis were matched for age and sex with the group receiving haemodialysis. Four children went on to receive transplants and were included in both this group and the group that had received transplants.

HEALTHY CONTROLS (N=31)

This group comprised children selected from ordinary schools and a general practice that were attended by patients being treated by hospital haemodialysis. There were 31 children (21 boys and 10 girls) with an age range of 2–18 years, mean 13). Although the subjects in the sample were not individually matched with those receiving dialysis, the three study groups were comparable for age and sex distribution. Full details about the last three groups have been published previously.[11]

Information was obtained from parents and children (except those who had received transplants) by interviews, and they and the schoolteachers completed questionnaires. For the present comparison, scores from Rutter A and B questionnaires and parental reports of child behaviour and emotional problems were used. Children's scores from the Birleson and Lipsitt questionnaires and information obtained at the interviews about their social life were compared, as were parental scores on the general health questionnaires and reports of parental problems with their mental health that were recorded at interview.

At the time of the assessment 19 (66%) of the patients were attending the transplant clinic every two to four weeks, and all but two of the rest were attending every four to eight weeks. The clinic is staffed by doctors and nurses known to the children from previous stages in their treatment, with additional input from a social worker and dietitian. Attention during clinic visits is paid both to physical and psychosocial aspects of the child's care, and parental support is also offered.

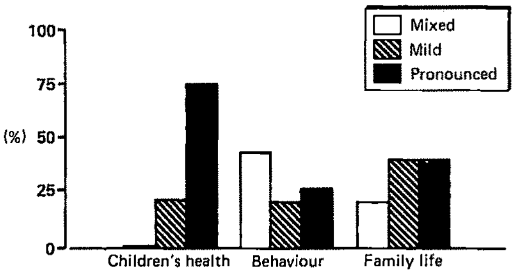
To assess the significance of differences among groups, the χ^2 or Fisher's exact test were used. Because we were primarily interested in comparing adjustment in the children in whom end stage renal disease was most severe, we computed statistics comparing the groups treated by transplant and haemodialysis. In the tables we also give, for reference, the corresponding figures for those not being dialysed and the healthy sample.

Results

Information was obtained from 25 out of 26 sets of parents in the first stage of the study, and in the second stage all 29 sets of parents and their children agreed to take part (23 boys and six girls, mean age 11·5 years, range 1–17). Two of the children were from one family. All but two of the patients had had experience of continuous ambulatory peritoneal dialysis or haemodialysis and four children had previously had transplants. The questionnaires were all completed at a relatively stable point in the children's condition, although six were receiving outpatient treatment for serious problems of graft rejection. Though they were still being maintained on increased doses of immunosuppressive drugs, the length of time that the grafts would survive in these patients was thought to be limited. The sample included some children with non-renal complications, including two with mental handicaps and one with rectal atresia who had a colostomy.

Parents were asked to rate the degree and direction of change in the child's health and behaviour, and in the quality of family life since transplantation. The figure shows that virtually all the parents (92%) reported improvements in their child's physical health and most considered the improvements to be considerable. Fewer but still a substantial number of parents (84%) reported changes in the child's behaviour in the time since the transplant. As many of the changes were mixed (both positive and negative) as for the better, but none was reported to be for the worse. A high percentage of parents (88%) reported changes in the quality of family life since transplantation. Of these, almost three quarters reported some improvement and none reported change for the worse.

As well as changes in these areas, we were interested in the parents' perception of their child's state at the time of assessment. The actual changes in health were reflected in parents' views of the child's current physical health, as only one third reported current problems, none of which was regarded as serious.



Percentage of parents reporting psychosocial improvements after transplantation (n=25). No changes for the worse were reported, and not all parents noted changes.

We asked parents to give their views about their child's behaviour and emotions at the time of assessment. Their comments were compared with those of parents of children not being treated with dialysis, undergoing hospital haemodialysis, and healthy controls (table 1). No parents in the transplant group felt that their children had serious difficulties. This compared favourably with both the other two groups of patients, in which more than one third of parents reported serious problems in behaviour. Children who had received transplants were often described at the time of assessment as 'normal in every way', or 'having only the ups and downs of a normal child'. The children were described as happier and less irritable than before transplantation; one young child was less aggressive and having fewer tantrums, and several adolescents were described as more confident and socialising better.

Reports were not universally positive, however, and 11 (39%) of the children had minor behavioural difficulties, most related to issues associated with illness, such as fears of going into hospital or of medical procedures—particularly the younger children. Unhappiness about appreance and poor growth were mentioned by parents of only two children as a cause of concern. Non-compliance with taking drugs was reported as a minor problem in two other children.

A similar number of parents (n=10, 38%) recorded behavioural problems on the parental Rutter A questionnaire. Seven children (70%) with high scores were considered by their parents to be having minor behavioural difficulties. Behavioural problems in the Rutter A questionnaire were more than twice as common in the group who had had transplants than in either the group receiving haemodialysis or the healthy group. Scrutiny of the individual items scored by parents of transplant children, however, showed that the deviance was largely made up of a number of mild behaviour symptoms, with severe symptoms rarely being scored. The general health questionnaire score for the one school leaver was high and the behaviour checklist scores for the two preschool children did not indicate an excessive number of problems. Two children (7%) were referred for psychiatric treatment.

The behaviour of the children with transplants at school, as assessed by the Rutter B questionnaire, did not differ appreciably from that of the healthy controls, but showed higher

Table 1 Child psychiatric adjustment

	Patients not treated by dialysis (n=22)	*Patients treated by hospital haemodialysis (n=22)*	*Patients treated by transplantation (n=29)*	*Healthy subjects (n=31)*
No (%) of parental reports of behavioural or emotional problems:				
Mild or dubious	3 (14)	5 (23)*	11 (38)*	11 (36)
Pronounced	8 (36)	10 (45)*	0*	4 (13)
No (%) scored on the Rutter behaviour questionnaire:				
'A' parental high score 13+	5/18 (28)	2/12 (17)	10/26 (39)	3/23 (13)
'B' teacher high score 9+	5/18 (28)	0	3/23 (13)	2/23 (9)

*p<0·02 (χ^2 test).

scores than for children on haemodialysis. Not all children were capable of completing the questionnaires, and 25 completed questionnaires on mood changes, self concept, and social contacts. Table 2 shows that their ratings were generally comparable with those of healthy controls, but they reported less severe and more mild worrying than those not being treated with dialysis or those receiving haemodialysis. They also had lower depressive scores on the Birleson scale, fewer had self concept scores indicative of low self esteem, and more of them indicated a favourable social adjustment as shown by having a special friend.

Reports of problems with 'nerves' were recorded for all sets of parents but only one parent of each child completed the general health questionnaire. Table 3 shows that there were fewer longer term mental health problems among parents of children with transplants compared with parents of children on haemodialysis, the difference for mothers being significant ($p<0\cdot05$). There is a less striking difference, but none the less superior parental current mental state in the group whose children had received transplants, with rates similar to those of the parents of the healthy group.

At the time of assessment two thirds of parents whose children had received transplants reported no problems in family life. They reported far less disruption caused by the illness, with more freedom, more energy, and time for normal family activities such as going away on holiday. Many parents said that their lives had become happier and better organised, with freedom from dialysis and dietary restrictions and fewer visits to hospital. They reported that they felt less tired and isolated, having more time for their own lives, including work and social activities. Four parents also commented spontaneously on improvements in sibling behaviour and school progress. One third of parents, however, reported some problems in family life, including two who had a second child with chronic renal failure, one who had a child on continuous ambulatory peritoneal dialysis, and the mother of a patient with a transplant and non-renal complications. Others reported some continuing anxiety about their children's health and the future of the transplant, and one parent said that the family had been left physically and mentally drained since removal of the pressure of coping with ambulatory peritoneal dialysis.

There was a lower percentage of intact families among those who had received transplants (61%) than among those receiving dialysis (77%), those not being treated with dialysis (91%), or healthy controls (81%). This included a pronounced excess in the number of stepparents in the group who had received transplants; six (21%) compared with none among those not being treated with dialysis or receiving haemodialysis, and two (6%) in the healthy group. In all but two cases remarriage was not a consequence of but had preceded the transplant.

At follow up after transplant parents were asked about the areas in which they required and were offered support, and the degree of their satisfaction with this. All but one (96%) noted that they received medical advice and information and 16 (64%) reported receiving support directed towards their own worries about the child's condition. Help with broader psychosocial issues was also commonly reported, including concern about the child's behaviour or education (n=16, 64%), practical difficulties such as travelling expenses to hospital (n=15, 60%) and with effects caused by the transplant on the family as a whole (n=10, 40%).

Parents sometimes commented spontaneously that although they had not needed or requested help, they thought it would have been available had they wanted it. Most (n=15, 60%) parents reported a lot of satisfaction with the amount of support and advice given at the clinic

Table 2 Child reports

	Patients not treated by dialysis (n=20)	*Patients treated by hospital haemodialysis (n=20)*	*Patients treated by transplantation (n=25)*	*Healthy subjects (n=28)*
No (%) who were worried:				
Mild	6 (30)	7 (35)*	21 (84)*	18 (64)
Pronounced	8 (40)	6 (30)*	0*	4 (14)
No (%) with high depression scores (Birleson Scale)	4 (20)	4 (20)	2/24 (8)	1 (4)
No (%) with low self concept scales (Lipsitt scale)	1 (5)	6 (30)	2/23 (9)	3 (11)
No (%) who had a special friend	11 (55)	6 (30)*	17 (68)*	23 (82)

*$p<0\cdot02$ (χ^2 test).

Table 3 Parental mental health

	Patients not treated by dialysis (n=20)	*Patients treated by hospital haemodialysis (n=20)*	*Patients treated by transplantation (n=27)*	*Healthy subjects (n=31)*
No (%) with mental health/nervous problems during last two years:				
Mothers	11/20 (55)	12/20 (60)*	7/27 (26)*	11/31 (36)
Fathers	0	3/19 (16)	2/24 (8)	1/26 (4)
No (%) with current mental distress: (general health questionnaire score 5+)				
Mothers	6/20 (30)	6/15 (40)	6/23 (26)	8/29 (28)
Fathers	2/9 (22)	3/10 (30)	0/5	2/11 (18)

*$p<0\cdot05$ (χ^2 test).

and four (16%) said they were fairly satisfied. The remaining six (24%) said they found the help offered satisfactory in some areas but not in others. Just under two thirds of parents said they did not need any more help from the hospital than that which had been offered, but nine (36%) said they would have liked some more help in certain areas, such as further information about the long term or side effects of medication. Two mothers mentioned their own continuing worries about symptoms and fears of rejection, saying they were sometimes too reticent to ask all the questions they would have liked.

Discussion

Our findings show that the improved physical health of children after transplantation is paralleled by pronounced improvements in their parents' perceptions of the children's behaviour and emotions, and their own mental health, and in the children's perceptions of their mood, self esteem, and social life. Our findings also indicate that children and families function better after transplantation compared with those receiving hospital haemodialysis treatment. The findings are consistent with our previous reports in illustrating the importance of considering the stage of illness and treatment when investigating the pschosocial effects of chronic illness in children, as these may give rise to different rates and types of psychological morbidity.[10 11]

We considered the possibility that our positive findings reflected some bias in parental reporting. Parents are aware of how much is invested in a transplant by the medical team, and may in some way be responding to what they consider are the team's expectations. They did describe very graphically and convincingly, however, the improvements that had occurred both in the children and in the quality of family life. Moreover, this would not account for the better child rated self esteem and social life scores in patients with transplants than in those receiving haemodialysis.

Our results on the beneficial psychosocial effects of transplantation are in keeping with those of previous studies that used less systematic measures.[4-6 19] Nevertheless, like previous authors of papers about social adjustment in children with transplants more than one year after transplantation,[8 9 19] we found increased scores on the behavioural questionnaire in the group after transplant. This seems to contradict the parents' perceptions of the improved behaviour and emotional state in these children, but we think that it probably reflects the fact that the behavioural difficulties were mostly only minor. In most children therefore the high scores were due to cumulative mild ones, and few severe symptoms were present.

The finding of minor behaviour difficulties in children after transplants confirms our results that children with end stage renal failure that is not severe enough to require haemodialysis or transplantation have behaviour problems that are not severe, although they are seen predominantly at school. It seems plausible that children also have some problems after transplantation, reflecting their difficulties in making the transition from being ill to being healthy.

The rate of behavioural disturbance leading to psychiatric assessment was smaller than that in a follow up study into adulthood of subjects who had undergone transplantation in childhood, in which this was reported as 22% during the five years preceding the study.[9] This could indicate either better general physical and psychological outcomes nowadays than when the transplants were carried out in the previous study, but it is also possible that the beneficial effects are not sustained. Longer follow up of our sample may reveal increased morbidity in early adulthood. The lower rate may, however, reflect the fact that there were close links between the paediatric and child psychiatry departments, which enabled regular discussions to take place between the psychiatrist and renal physicians. Problems about any patients were discussed as they arose in the multidisciplinary group and a plan for intervention agreed upon. This often obviated the need for formal psychiatric intervention.

Much has been made in previous reports of concerns by children about their appearance and it is surprising that such problems were not more widely reported in our study.[8 9 19] Issues such as short stature, hirsutism, and body image emerge quite regularly as areas of concern, and it may be that interviews with the children themselves would have been necessary to assess fully the degree of these concerns. The children did report some worries, which were perhaps related to appearance and growth as well as to fears connected with admission to hospital (as reported by parents). For the most part, however, these worries did not seem to be handicapping. This does not detract from the need for attention to be given to subjects in whom specific concern is identified to reduce the likelihood of it affecting long term adjustment.

Our findings on child adjustment have to be viewed against the background of the improvements in the quality of family life and parental mental health, and the high levels of support offered and taken up by families at the transplant clinic. While there were some unmet needs, the degree of parental satisfaction was generally good. The support encompassed not just physical issues but also psychological and social ones and our results may not have been so favourable without it. The minor problems in psychological adjustment that the children still had could have escalated without appropriate support and guidance from staff at the clinics. A paediatric team that is aware of psychosocial issues will be able to meet many of the needs of transplant patients, but should be able to make specific referrals where appropriate.

Finally, there remains a number of children whose transplants fail, or for whom transplantation is not a possible option and other treatments such as continuous ambulatory peritoneal dialysis, or home or hospital haemodialysis, are required either permanently or as a stage in treatment. The differential effects of these treatments on social and psychological adjustment have not been investigated but are worth clarifying in view of our findings that it is possible to identify different psychosocial functioning among children at various stages of treatment.

We thank all the children and parents who took part in the study, the staff at Booth Hall Children's Hospital renal unit for their help, and the British Kidney Patients' Association, without whose help this work would not have been possible.

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Inhaled frusemide

Inhaled frusemide reduces both the early and the late bronchoconstrictor responses of asthmatic subjects to antigen and protects against bronchoconstriction induced by exercise, nebulised distilled water, and metabisulphite. It is not known whether this protective effect is a result of an action on the epithelial cell, inflammatory cells, nerve endings, or smooth muscle. Workers in Nottingham (Knox and Ajao, *Thorax* 1990;45:856–9) studied both bovine and human airway smooth muscle in vitro. They found that frusemide did not inhibit the smooth muscle contraction induced by histamine, potassium chloride, or hyperosmolar saline and concluded that the effect of frusemide is unlikely to be due to a direct action on airway smooth muscle.

To the best of my knowledge there are as yet no reports of the therapeutic use of inhaled frusemide in asthma. The treatment of asthma is one of the great therapeutic advances of the last 25 years but new work appears constantly,[1–4] and the near future promises to be equally rewarding.

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White sponge naevus and ocular coloboma

S Wright, I S Levy

Abstract

White sponge naevus occurred in association with coloboma of the iris in six members of one family, across three generations. The association of these two dominantly inherited conditions has not to our knowledge previously been described.

There are several previous reports of an association between coloboma of the eye and other developmental abnormalities.[1–4] Colobomas are usually inherited as an autosomal dominant characteristic.

White sponge naevus was first described by Cannon in 1935,[5] but has a number of other names including hereditary leucokeratosis[6] and white folded gingivostomatitis.[7] The condition is also inherited as an autosomal dominant characteristic, but has not to our knowledge been described in association with ocular coloboma.

We report a family pedigree in which there is an association between white sponge naevus and iris coloboma; it confirms previous reports that both these congenital abnormalities are inherited in an autosomal dominant manner.

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Case reports

CASE 1

A boy aged 3 years (IV.6 in fig 1) was referred to the department of dermatology at this hospital because of sparse hair. When seen in the clinic, his hair was noted to be sparse, but the discrete areas of hair loss described by his mother were not seen. He had bilateral inferomedial colobomas of the iris (fig 2). Examination of his mouth showed a creamy white folded hyperkeratosis particularly affecting the buccal mucosa, but also the tongue, and pharynx. He was below the 3rd centile for height and below the 10th centile for weight, but a full developmental assessment suggested that this was a constitutional short stature. Microscopy of his hair was normal. Slit lamp examination of his eyes and indirect ophthalmoscopy showed a normal retina and lens. Culture of mouth swabs failed to grow *Candida* spp and radiographic assessment showed that his bone age was consistent with his chronological age. At the age of 2·1 years he had a strangulated left indirect inguinal hernia repaired.

CASE 2

The mother of case 1 (III.4 in fig 1), who was aged 21 years, was noted to have bilateral iris colobomas at birth. During school dental examinations she had a folded, creamy white hyperkeratosis of the buccal mucosa (fig 3), which on histological examination was identical

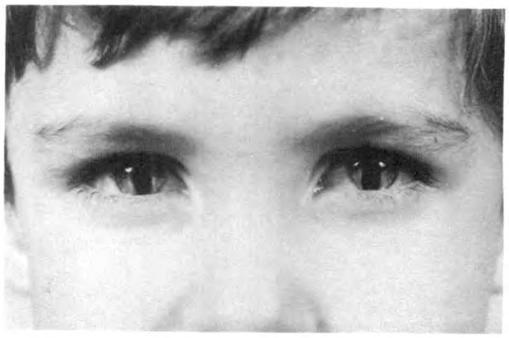
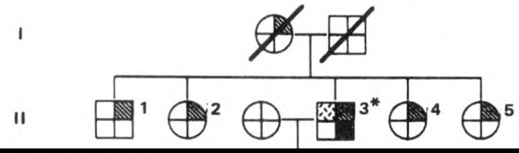


Figure 2 Eyes of case 1 showing bilateral inferomedial coloboma of the iris.



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to that of her son. Despite persistently negative swabs, she was treated on several occasions with anticandida preparations, but with no success. She had no oral symptoms. Vaginal and rectal mucosa were unaffected.

Slit lamp examination and indirect ophthalmoscopy with a dilated iris showed a normal lens and retina. A biopsy specimen of the oral mucosa showed an acanthotic epithelium with intracelluar oedema and some vacuolation in the outer half. Maturation and stratification were normal, and there was no dyskeratosis. There was a light superficial dermal lymphocyte infiltrate (fig 4).

A family history was obtained from case 2, who was aware that her paternal grandmother had the same oral abnormality. The ocular abnormalities were present in her father's right eye. He was also examined and found to have coloboma limited to the iris and oral findings identical to those of his daughter. Subsequently a number of visits to various members of the family have enabled the construction of a reasonably complete family tree (fig 1).

In generation II, all five siblings have oral lesions and one out of five has ocular coloboma. In generation III, six out of seven siblings have oral lesions and four out of seven have iris coloboma. Every member of the family with iris coloboma also has white sponge naevus, although some members with white sponge naevus do not have iris coloboma. In the seven children so far born in generation IV, four have white sponge naevus and one of these four (the index case) also has bilateral iris colobomas. Three children in generation IV have died in infancy, one of agenesis of the left heart, one with Fallot's tetralogy who died of infection after a Blalock shunt, and the other one of unknown cause during the first year of life. One surviving child has a small ventricular septal defect. Of the eight men with white sponge naevus in the whole family pedigree, five have had inguinal hernias reduced surgically during early childhood. Nothing remarkable was noted about these hernias at the time of operation. High resolution karyotyping of two adult members of the family is normal.

One of the authors (SW) has personally examined 10 affected family members (fig 1). No family member has been listed as affected unless they have either been seen by the author or have had the signs confirmed by at least two members of the family. Those family members who have not been examined are either out of the country or have refused to consent to physical examination.

Discussion

The differential diagnosis of white sponge naevus includes pachyonychia congenita, dyskeratosis congenita, Darier's disease, lichen planus, oral candidiasis, and hereditary benign intraepithelial dyskeratosis. White sponge naevus is usually congenital but may appear at any stage of infancy or childhood, and occasionally in adolescence. The oral lesions are typically widespread, affecting the palate, gingiva, floor of the mouth, and tongue as well as the buccal mucosa and comprise a thickened, folded, or corrugated epithelium with a spongy texture and a white opalescent hue. The condition is asymptomatic. This clinical picture alone is sufficient to make a positive diagnosis, and the histological features confirm it. The appearances described in fig 4 are typical, with, in particular, no dyskeratosis. There is acanthosis and usually more parakeratosis than is seen in this case. Oedema throughout the spongy layer is associated with vacuolation of keratinocytes.

[redacted]

or eighth week of fetal life, and may therefore affect any or all of the neuroectodermal structures derived from the optic vesicle—the iris, the ciliary body, choroid, optic disc, or optic nerve. They have been described in association with a variety of neuroectodermal syndromes, perhaps the best known of which is the Biemond syndrome II, comprising pituitary dwarfism associated with mental retardation, obesity, hypogonadism, postaxial polydactyly, and colobomas. Recently attention has been focused on the CHARGE association of colobomas, heart disease, atresia choanae, retarded growth, genital hypoplasia, and ear abnormalities. Iris colobomas have not to our knowledge been described in association with white sponge naevus, but the extent of the association in the family reported here serves to establish it as a real association.

The coexistence of white sponge naevus and iris coloboma in this family and the fact that all family members with either unilateral or bilateral iris coloboma also have white sponge naevus suggest that it is a single gene autosomal dominant disorder. If this were the case white sponge naevus would be expressed in all gene carriers, whereas iris coloboma would show variable expression.

Alternatively there could be two linked genes which have become separated by recombination in those family members who have white sponge naevus but not iris coloboma, but remain linked in those family members who show both characteristics. This seems less likely for several reasons. If iris coloboma resulted from a single dominant gene, one would expect it to be an isolated finding in some family members. As 10 of 19 family members have white sponge naevus without iris coloboma, the recombination rate of the proposed two genes would be roughly 50%; this is not consistent with the genes being in close linkage.

None the less it is of interest that iris coloboma has not been described in the same patient as white sponge naevus before this family. The condition is visible, and white sponge naevus is unlikely to be missed at regular school dental examinations.

It is intriguing that the ocular coloboma in all the affected members of this family affects the iris only, as any part of the eye derived from the optic vesicle may theoretically be affected. This implies that the embryological development of the iris may be genetically separate from that of the rest of the chorioretinal tract.

The fact that three boys in generation IV have congenital heart disease and that inguinal hernia has occurred in infancy in at least five out of eight male infants suggest that a search among families with white sponge naevus or iris coloboma, or both, should be undertaken to find out if this apparent association is more than coincidence.

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Gonadal function after allogenic bone marrow transplantation for thalassaemia

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Abstract

Thirty prepubertal patients with thalassaemia major (15 boys and 15 girls) aged from 9·3 to 17·2 years (mean 12·9) who had successfully undergone allogenic bone marrow transplantation were studied. Before the transplant all patients were given short courses of high doses of busulphan (total dose 14 mg/kg) followed by cyclophosphamide (total dose 200 mg/kg). Pituitary gonadal function was asssessed between 0·7 and 5·1 years (mean 2·3) after bone marrow transplantation. Increased gonadotrophin concentrations indicating gonadal damage were found in 80% of the girls, probably as a result of the chemotherapy. In all the prepubertal boys the basal follicle stimulating hormone and luteinising hormone concentrations were normal. Most of the boys had reduced gonadotrophin and testosterone responses after gonadotrophin releasing hormone and human chorionic gonadotrophin tests. This could have been the result of iron overload but the effect of cytotoxic agents cannot be excluded. These findings emphasise the need for vigilant long term follow up of thalassaemic patients treated with cytotoxic chemotherapy for bone marrow transplantation so that those requiring hormone replacement can be identified and treated.

Bone marrow transplantation is a realistic therapeutic option for patients with thalassaemia major.[1] Intensive short courses of chemotherapy are given before transplantation to eradicate the recipient's own marrow and to produce sufficient immunosuppression to permit allogenic grafting. The adverse effects of chemotherapeutic agents on the gonads have been well documented in adolescents and adults, but less is known about the effects in children.[2–4]

Sanders *et al* have now provided much needed data on subjects with aplastic anaemia or leukaemia after bone transplantation,[4–6] but there have been no reports about endocrine function in thalassaemic patients after successful bone marrow transplantation. This is particularly important, as most of these patients have some degree of endocrine dysfunction before transplantation.

In this report we provide data about pituitary gonadal function in a group of prepubertal thalassaemic patients who are long term survivors of bone marrow transplantation.

Patients and methods

We studied 30 prepubertal patients with thalassaemia major (15 boys and 15 girls) aged from 9·3 to 17·2 years (mean 12·9) who had successfully undergone allogeneic bone marrow transplantation in the department of haematology at the Ospedale Muraglia, Pesaro, Italy. Sibling donors matched at the major histocompatibility loci were used for transplantation.

Before transplantation the parents were informed of the risks and potential benefits compared with those of conventional treatment with blood transfusions and chelation with desferrioxamine mesylate.

The patients were prepared for the transplant with busulphan (3·5 mg/kg body weight) given orally three times a day on four consecutive days, followed by cyclophosphamide (50 mg/kg body weight) given intravenously on each of the next four consecutive days, a regimen modified from that first described by Santos.[7]

Marrow was infused 36 hours after the course of cyclophosphamide. Prophylaxis against graft versus host disease (GVHD) consisted of methotrexate in one patient and cyclosporin in 29 patients.

Three patients developed chronic GVHD after transplantation and were treated with long courses of corticosteroids, cyclosporin, and azathioprine. Pituitary gonadal function was assessed from 0·7 to 5·1 years (mean 2·3) after bone marrow transplantation, by assaying the concentrations of follicle stimulating hormone and luteinising hormone in blood before and 20, 40, 60, and 120 minutes after intravenous injection (50 μg/m^2) of gonadotrophin releasing hormone (Relisorm, Biodata). Plasma concentrations of luteinising hormone and follicle stimulating hormone were measured in duplicate with commercial immunoradiometric (IRMA) kits (Serono Laboratories) as follows: luteinising hormone—first international reference preparation 68/40, with intra-assay coefficients of variation of 9% at 0·5 IU/l, and 3·2 at 50 IU/l; and follicle stimulating hormone—second international reference preparation 78/549, with intra-assay coefficients of variation of 11% at 0·5 IU/l and 2·9% at 50 IU/l.

The basal and peak hormonal responses were compared in the thalassaemic patients and 14 prepubertal controls (seven boys and seven girls) mean (SD) age 10 (1) years (tables 1 and 2).

Leydig cell function in the boys was assessed by measuring the plasma testosterone concentration by radioimmunoassay (RIA) before and 72 hours after stimulation with human chorionic gonadotrophin 2000 units intramuscularly.

Other variables measured were serum basal 17β-oestradiol in the girls, serum thyroid

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Table 1 Gonadotrophin releasing hormone test: plasma gonadotrophin concentrations and serum basal oestradiol in 15 female thalassaemic patients who had undergone bone marrow transplantation

Case No	*Luteinising hormone (IU/l)*		*Follicle stimulating hormone (IU/l)*		*Oestradiol (pmol/l)*
	Basal	*Peak*	*Basal*	*Peak*	
1	1·8	12·6	12·0	22·0	<36·7
2	<0·5	<0·5	<0·5	1·0	<36·7
3	<0·5	<0·5	<0·5	1·7	<36·7
4	0·5	2·0	1·7	2·7	<36·7
5	45·0	200·0	114·0	140·0	<36·7
6	34·3	134·0	103·0	140·0	<36·7
7	2·2	6·1	10·0	13·3	<36·7
8	3·3	11·1	12·8	16·7	<36·7
9	4·5	16·0	15·5	24·3	<36·7
10	13·0	39·0	48·0	63·0	<36·7
11	12·6	50·2	62·2	88·0	<36·7
12	3·5	13·3	17·6	23·8	<36·7
13	9·7	38·4	43·8	57·3	<36·7
14	4·9	14·8	16·1	20·8	<36·7
15	2·4	7·9	9·6	12·4	<36·7

Mean (SD) reference ranges:
Luteinising hormone—basal 0·5 IU/l; peak 2·8 (1·6) IU/l; range 1·3–6.
Follicle stimulating hormone—basal 1·9 (1·4) IU/l, range 0·5–4·3; peak 10 (2·7) IU/l, range 7·9–14.
Oestradiol—basal <36·7 pmol/l.

Table 2 Gonadotrophin releasing hormone test (plasma gonadotrophins) and human chorionic gonadotrophin test (serum testosterone) in 15 male thalassaemic patients who had undergone bone marrow transplantation

Case No	*Luteinising hormone (IU/l)*		*Follicle stimulating hormone (IU/l)*		*Testosterone (nmol/l)*	
	Basal	*Peak*	*Basal*	*Peak*	*Basal*	*Peak*
16	0·5	4·2	1·6	11·2	69	208
17	0·5	6·9	2·9	6·6	49	482
18	0·6	0·8	1·1	2·3	69	69
19	0·5	0·7	0·5	1·0	49	270
20	0·5	0·5	1·0	1·0	69	69
21	0·5	0·9	0·5	1·9	38	374
22	0·9	3·4	1·2	1·8	125	277
23	0·5	2·3	0·5	0·6	69	250
24	0·8	4·2	0·7	2·8	107	728
25	0·5	1·7	1·1	1·0	32	180
26	0·5	1·8	1·6	2·5	104	222
27	0·5	0·6	0·5	0·6	32	184
28	0·5	1·1	0·5	1·2	69	139
29	0·5	0·5	0·5	0·5	80	166
30	0·6	1·3	0·5	0·7	69	267

Mean (SD) reference ranges:
Luteinising hormone—basal 0·58 (0·14) IU/l; range 0·5–0·9; peak 3·6 (2·4) IU/l; range 1·4–8·5.
Follicle stimulating hormone—basal 1·6 (1·1) IU/l, range 0·5–3·1; peak 2·7 (1·1) IU/l, range 1·8–5·8.
Testosterone—basal 83 (38) nmol/l, range 32–139; peak 610 (198) nmol/l, range 368–1002.

Table 3 Details of female thalassaemic patients who have undergone bone marrow transplantation

Case No	*Interval between transplantation and study (years)*	*Age at study (years)*	*Height (cm)*	*Weight (kg)*	*Bone age (years)*	*Serum ferritin (μg/l)*
1	1·2	9·3	130·0	25·3	8·0	925
2	3·7	9·4	135·1	32·0	10·7	2905
3	1·0	11·8	127·0	23·3	10·0	2125
4	3·0	12·0	135·9	29·7	12·3	3150
5	1·3	12·5	140·0	38·0	10·0	1840
6	2·5	12·8	144·8	29·0	12·0	4030
7	3·3	13·0	139·3	35·5	10·5	2085
8	4·6	13·3	147·5	36·0	12·0	935
9	1·8	13·3	152·3	51·7	11·5	1380
10	2·8	13·5	142·0	55·0	11·8	2050
11	2·2	13·9	160·2	61·8	14·3	1175
12	3·3	14·0	147·9	35·9	13·0	2120
13	2·3	15·0	145·9	32·9	11·1	5500
14	0·6	15·5	152·0	58·2	12·3	2705
15	2·0	16·8	152·0	46·5	12·5	1795

stimulating hormone, thyroxine, bone age, and serum ferritin concentrations using radioimmunoassay as previously described.[8] Sexual maturation was assessed using the criteria laid down by Tanner.[9] Bone age was estimated in all patients by the same observer (VDS) using the TW2 method.[10] Results are expressed as mean (SD). Statistical analysis was by the Wilcoxon rank sum test; probabilities of <0·05 were accepted as significant.

Results

Table 3 and 4 show the main clinical and laboratory features in female and male thalassaemic patients. All had normal thyroid function.

GONADAL PITUITARY FUNCTION IN GIRLS (table 1)
Before bone marrow transplantation the plasma gonadotrophin concentrations (assayed by RIA with polyclonal antibody) of all 15 patients were in the middle to lower parts of the reference ranges: luteinising hormone—mean 2·8 IU/l, range 1·5–5·0, controls 3·1 IU/l, range 1·6–4·2; follicle stimulating hormone—mean 2·9 IU/l, range 2–6, controls 4·2 IU/ml, range 3·1–6·2.

After bone marrow transplantation 12 (80%) had evidence of primary ovarian dysfunction as judged by raised basal serum gonadotrophin concentrations. The patients' basal values of luteinising hormone ranged from <0·5 to 45·0 IU/l (controls 0·5) and basal values of follicle stimulating hormone from <0·5 to 114 IU/l (controls 0·5–4·3). After injection of gonadotrophin releasing hormone peak luteinising hormone and follicle stimulating hormone concentrations were usually considerably higher than in controls except in cases 2 and 3 who also had low basal values, and in case 4, who had an isolated low follicle stimulating hormone response.

The basal oestradiol values in both the thalassaemic patients and the prepubertal controls were below the sensitivity of the assay (36·7 pmol/l); hence they could not be analysed.

There was no association between increased gonadotrophin concentrations and the age of the patients. Serum ferritin concentrations ranged from 925 to 5500 μg/l, mean 2314 μg/l (control: range 14–148 μg/l).

GONADAL PITUITARY FUNCTION IN BOYS (table 2)
Before bone marrow transplantation basal gonadotrophin concentrations of all 15 patients were in the middle to lower parts of the reference ranges: luteinising hormone—mean 2·3 IU/l, range 2–6; controls 3·5 IU/l, range 1·7–5·7; follicle stimulating hormone—mean 2·4 IU/l, range 1–3·5; controls 3·8 IU/l, range 1·7–6·3. After transplantation all had basal luteinising hormone and follicle stimulating hormone concentrations within the control range: luteinising hormone 0·5–0·9 IU/l (controls 0·5–0·8), and follicle stimulating hormone 0·5–2·9 IU/l (controls 0·5–3·1).

After the gonadotrophin releasing hormone test three patterns of response were observed. Three patients (22, 24, and 26) had stimulated gonadotrophin concentration within the control range, two (16 and 17) showed a follicle stimulating hormone response greater than the controls, and 10 (18–21, 25, and 27–30) had significantly lower luteinising hormone or follicle stimulating hormone concentrations (or both)

Table 4 Details of male thalassaemic patients who have undergone bone marrow transplantation

Case No	*Interval between transplantation and study (years)*	*Age at study (years)*	*Height (cm)*	*Weight (kg)*	*Bone age (years)*	*Serum ferritin (µg/l)*
16	1·5	6·2	118·0	25·1	7·0	735
17	5·1	10·0	137·6	34·5	11·0	2490
18	1·9	10·1	127·5	29·0	10·0	3210
19	3·4	10·0	138·0	45·5	10·4	1010
20	1·7	10·4	134·0	29·0	10·0	2835
21	3·3	10·5	130·5	26·5	11·1	1485
22	3·0	13·0	166·5	64·5	14·0	1970
23	1·7	13·7	149·0	38·5	11·8	6325
24	2·5	14·1	136·7	25·0	10·3	5750
25	2·2	15·0	143·7	32·4	12·6	2125
26	2·2	15·3	149·3	47·7	13·1	1945
27	2·0	15·3	159·0	47·3	14·8	4045
28	1·3	15·5	147·5	36·5	11·6	4140
29	2·1	16·8	150·0	47·2	13·2	1460
30	1·4	17·2	148·5	40·0	14·6	1605

than the prepubertal controls: luteinising hormone 1·04 (0·58) IU/l (controls 3·6 (2·4)) (p<0·01), and follicle stimulating hormone 1·08 (0·59) IU/l (controls 2·7 (1·1)), (p<0·01).

The basal serum testosterone concentrations in the patients did not differ significantly from those of prepubertal controls: 69 (27) nmol/l compared with controls 83 (38). Intramuscular injection of human chorionic gonadotrophin produced a variable response. Three patients (cases 17, 21, and 24) responded normally (range 413–728 nmol/l), 10 (cases 16, 19, 22, 23, and 25–30) had an inadequate response (range 139–277 nmol/l); two (cases 18 and 20) showed no response. The normal basal and peak testosterone levels are given in the footnote to table 2. Serum ferritin concentrations ranged from 735 to 6325 µg/l (mean 2742) (control range 14–148).

Discussion

Increased gonadotrophin concentrations indicating gonadal damage were found in most of the thalassaemic girls but those in the prepubertal thalassaemic boys were within the reference range. A normal follicle stimulating hormone concentration before puberty, however, does not preclude germinal epithelial damage. A secondary abnormal increase in gonadotrophin concentrations after the onset of puberty has been reported after treatment in prepubertal boys with acute lymphatic leukaemia or Hodgkin's disease,[11] and in patients with gonadal dysgenesis[11] or Klinefelter's syndrome.[13]

In most prepubertal thalassaemic boys the gonadotrophin and testosterone responses were reduced after the injections of gonadotrophin releasing hormone and human chorionic gonadotrophin. This has also been reported in thalassaemic patients who have not undergone bone marrow transplantation,[14–17] and has been attributed to iron deposition in the pituitary and to chronic hepatitis.[15 16] Iron overload could be a factor in our patients but a direct effect of cytotoxic agents on the gonads cannot be excluded.

Our observations in prepubertal patients show that whereas there is no obvious gonadal damage in boys as a result of the chemotherapy used before bone marrow transplantation, there is serious damage to the gonads on girls. It is likely that this is the result of the toxic effects of the drugs given in the conditioning phase, but because of the combinations of drugs it is difficult to identify which one was responsible for the gonadal damage.

Our patients received short term chemotherapy with cyclophosphamide (total dose 200 mg/kg) and busulphan (total dose 14 mg/kg) before allogeneic bone marrow transplantation. Cyclosporin or methotrexate were used for prophylaxis against GVHD. Others have reported that ovarian damage seems to be correlated with the dose of cyclophosphamide given. Thus in patients with aplastic anaemia and leukaemia 500 mg/kg given before bone marrow transplantation caused ovarian failure, whereas 200 mg/kg seemed to have little toxic effect in 18 prepubertal girls whose subsequent pubertal development and menstrual function were normal.[18] It has been suggested, however, that cyclophosphamide results in ovarian dysfunction when used in combination with other drugs.[19] In rats busulphan given during pregnancy causes the selective disappearance of fetal oocytes.[20] A similar effect has been reported in humans.[21] The effects of cyclosporin on the gonads in humans are not yet known, although dysfunctional and structural injury have been shown in the ovaries of rabbits given the drug.[22]

In interpreting our data it is important to remember that even in thalassaemic patients who have not had bone marrow transplantation studies of histological appearance and hormonal function have shown a reduction in the number of primordial follicles[23 24] and impaired gonadal function.[25]

There was a wide variation in the increase of gonadotrophins found in the female patients that we studied. Transitory increased secretion has been reported in leukaemic children during induction chemotherapy,[26] and in two prepubertal girls treated with spinal irradiation.[27] It is unlikely that an acute effect of chemotherapy influenced the investigation of our patients. The wide range luteinising hormone and follicle stimulating hormone values in our patients might be explained by previous pituitary involvement, which we have found to be common in thalassaemic patients who have regularly been transfused.[25]

Our findings have several implications. Successful bone marrow transplantation is considered a radical cure for thalassaemia. The results of this study, however, seem to indicate that it has the serious drawback of gonadal damage, which will have a deleterious effect on the quality of life. There is no doubt that this must be taken into account when discussing the pros and cons of bone marrow transplantation with the patient and parents. It must also be remembered, however, that when thalassaemia major is treated in the traditional manner, delayed puberty or absence of puberty is the most common endocrine disorder[28] and many girls—even though they start to menstruate—will have secondary amenorrhoea.[8] There are few thalassaemic girls who are fertile or in whom fertility can be induced. In addition, prolonged follow up after bone marrow transplantation is necessary before it is certain that gonadal damage is permanent, because some leukaemic subjects have undergone pubertal development in spite of the fact that their gonads have been damaged by treatment before puberty.[29]

This study is the first that we know of on pituitary gonadal function in prepubertal thalassaemic patients after successful bone marrow transplantation. Our data indicate that more experimental work is needed to design conditioning chemotherapy that will be both effective and non-toxic, and to find out how to prevent damage by cytotoxic agents to the patient's gonads. Glode *et al* found that in mice giving [D-]leu]-des-Gly-NH_2 proethylamide gonadotrophin releasing hormone protected the testes from damage induced by cyclophosphamide.[30] It is important that functional studies of the hypothalamic pituitary gonadal axis and long term surveillance should be carried out in thalassaemic patients who have undergone bone marrow transplantation. Only in this way can those requiring hormone replacement be identified and treated and this would avoid both the impairment of growth and sexual development that affect their social life.

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Development of night time temperature rhythms over the first six months of life

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Abstract

Continuous recordings of night time rectal temperature were made at regular intervals over the first six months of life in 49 babies. In the first two weeks of life rectal temperature changed little overnight, but by 6 weeks of age rectal temperature at bedtime was significantly higher than later in the night. By around 12 weeks of age sleeping deep body temperature fell below 36·5°C, and by 16 weeks of age all babies exhibited a consistent rhythm of rectal temperature. This fell by about 0·8°C within two hours of bedtime, and then remained low until an hour or two before waking. As babies got older the mean interval between bedtime and first disturbance of parents got longer. Sleeping rectal temperature fell below 36·5°C at about the time babies slept for seven hours. From 6 weeks of age, as individual baby's rectal temperatures fell more with sleep, sleep got longer.

By 4 months of age babies exhibit a characteristic pattern of change of deep body temperature at night. It falls from above 37°C at bedtime to around 36·4°C during the first two hours, remains low for a few hours, and then rises gradually again before waking.[1] The rapid fall in temperature is associated with sleep so its precise timing is related to bedtime, but the extent of fall is greater during sleeps at night than during the day, even when they are of similar duration.[2] This suggests that a circadian rhythm has begun to develop, though its expression is still affected by individual sleeping patterns, which may vary considerably from one infant to another at this age.

The rate and extent of fall of temperature is unaffected by ambient temperature and thermal insulating of clothing and wrapping within the range normally chosen by parents[3]; this indicates that the pattern is endogenous and maintained by active thermoregulation if necessary.

This pattern of temperature change does not occur in the newborn, so it must develop during the first few weeks of life. There are some reports that suggest a rhythm appearing around 1–2 months of age,[4] but there are no reports of continuous recordings on reasonable numbers of babies. In this study, therefore, we have used continuous recording techniques in a combined longitudinal and cross sectional design to observe the development of temperature rhythms in a good sample of babies and have related the temperature patterns to sleep and thermal environment.

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Subjects and methods

Subjects were recruited at birth in the Leicester General and Royal Infirmary maternity hospitals. The purpose of the study was explained to parents and permission sought to make continuous night time recordings of temperature at two to four week intervals over the next six months. If parents agreed basic perinatal data were collected from hospital notes, and in most cases a recording of the baby's body temperature (see below) was made before leaving the hospital.

The subsequent inter-recording intervals for each baby were adjusted so as to try and record from roughly equal numbers of babies in each two week age band from 0 to 24 weeks. Inevitably, some babies were lost to the study. They were replaced with others on which recording started at a later age.

On each recording night the baby was visited at home in the early evening, weighed naked, and temperature probes attached. One soft probe, inserted 5 cm from the anal margin, measured rectal temperature, and other probes recorded skin temperature on the head and either the abdomen or shin. Only rectal temperature data will be discussed in this paper. A fourth probe measured room temperature at the cot side. All probes were connected to a Grant Squirrell data logger, set to sample at one minute intervals throughout the night. These techniques have been demonstrated to be safe,[1] and full ethical committee permission was obtained for the study.

Parents were asked to keep a diary of events such as feeds, nappy changes, periods of waking, etc, throughout the period of recording. At each visit a note was made of feeding regimens, and information collected from health diaries kept by parents of illness in the baby and family. At each recording, note was made of items of clothing and wrapping around the baby, so that a thermal insulation, or 'tog value' could be calculated using data supplied by the Shirley Institute, Manchester.

The next day data were down loaded from the data loggers to a computer and scrutinised for evidence of technical problems such as loss of probes. Only unblemished data were analysed further. Mean rectal temperatures, together with standard errors, were collated at various times after bedtime for babies in each two week age band. Statistical comparisons were made using Student's *t* tests, paired where appropriate.

Results

SUBJECTS

A total of 49 babies were recruited to the study, and 109 usable temperature recordings were made. Probes were lost during a further seven recordings; these were approximately evenly distributed over the age ranges studied. A total of 41 babies were born after 36 weeks' gestation,

Thermal environment of babies studied. Results are mean (SEM)

	Age (weeks)										
	0–2 (n=19)	*2–4 (n=11)*	*4–6 (n=12)*	*6–8 (n=7)*	*8–10 (n=11)*	*10–12 (n=9)*	*12–14 (n=11)*	*14–16 (n=9)*	*16–18 (n=5)*	*18–20 (n=8)*	*20–24 (n=7)*
Tog value	7·2 (0·78)	12·31 (1·48)	10·7 (1·3)	10·08 (2·3)	11·36 (1·35)	12·81 (1·03)	11·7 (1·5)	11·35 (2·2)	10·68 (1·9)	10·68 (0·96)	11·45 (1·3)
Room temperature (°C):											
Minimum	20·45 (0·64)	19·99 (1·57)	18·20 (0·75)	18·25 (0·5)	16·82 (0·62)	18·53 (0·5)	14·99 (0·92)	17·55 (0·8)	17·67 (0·52)	17·98 (0·8)	15·29 (0·7)
Maximum	23·85 (0·52)	23·95 (0·99)	22·23 (0·68)	21·82 (0·54)	22·12 (0·62)	21·59 (0·5)	21·59 (0·8)	21·81 (0·8)	22·14 (0·8)	22·51 (0·8)	21·32 (0·6)

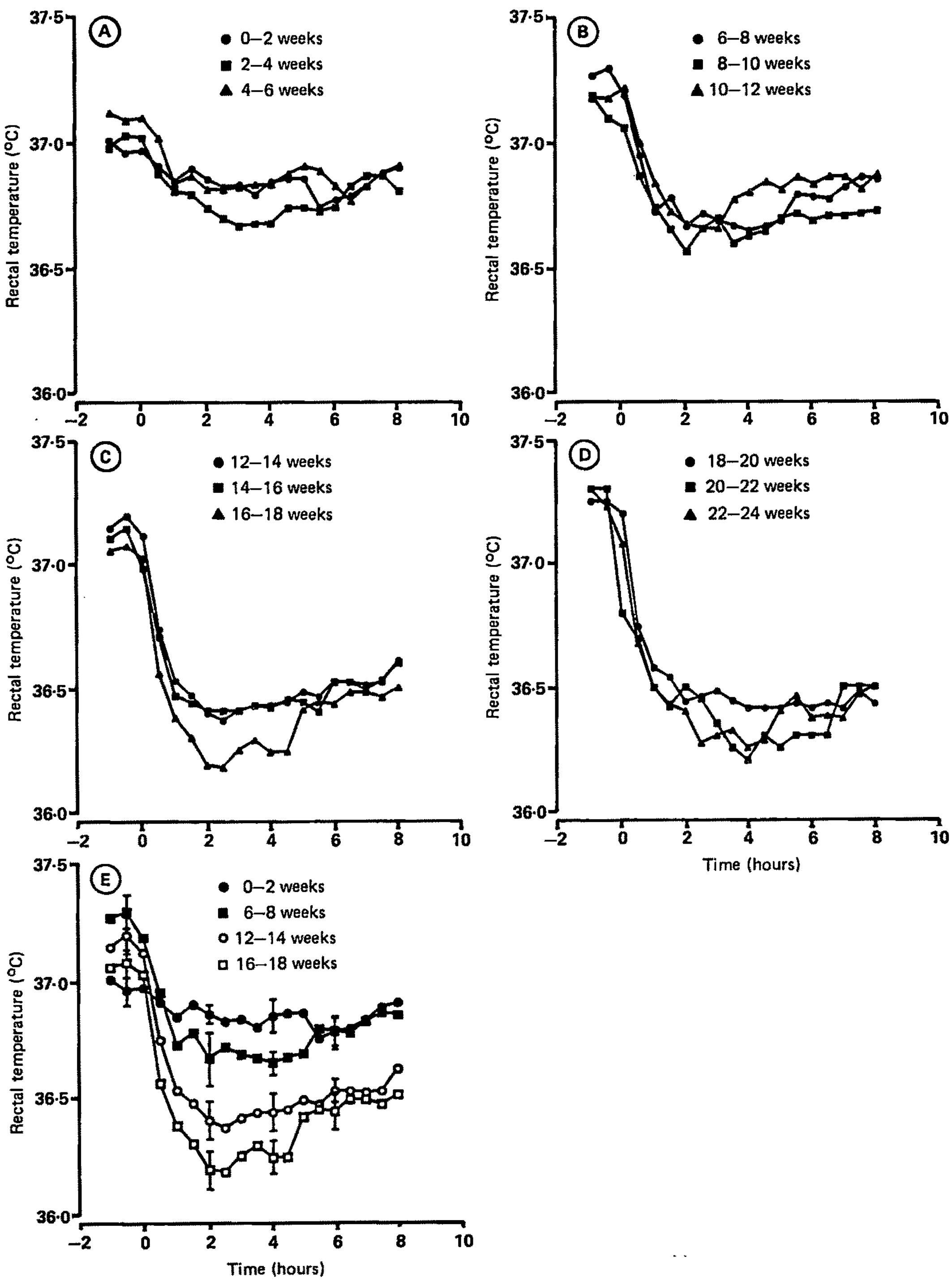

Figure 1 Changes in rectal temperature overnight in babies of different ages. In each case all valid recordings on babies in each two week age band were averaged relative to bedtime. Standard errors are mostly not presented on the figures for clarity; they range from 0·03–0·11°C, typically 0·06°C. Figures A to D show all data, E shows ages selected to emphasise significant points.

five between 34 and 36 weeks, and three between 32 and 34 weeks. There were no obvious differences in the data from the small number of babies born prematurely. Twenty three of the babies were recorded on at least four occasions, six recorded three times, and the remainder recorded once or twice to increase numbers in the later age ranges. Most of the recordings over the critical age range of 4–16 weeks formed part of a series of at least four.

THERMAL ENVIRONMENT

The table shows the minimum and maximum room temperatures and tog values of clothing and wrapping for babies of different ages. The data for babies 0–2 weeks old include some measurements made in hospital (including the special care baby unit occasionally) where ambient temperatures are often high and babies are lightly wrapped. Thereafter all measurements were at home. Babies at home up to 1 month old were kept in slightly warmer rooms, and covered with more insulation, than older babies. From about 6 weeks of age parental behaviour seemed to stabilise, and both room temperatures and tog values did not change significantly as babies got older. These observations were made over a full 12 months, and so contain data from summer and winter, though the seasonal differences were not great.

RECTAL TEMPERATURES

Averaged data for various ages are presented in fig 1. In the first two weeks of life rectal temperature varied little overnight, however, by six weeks the temperature was over 37°C at bedtime and fell to about 36·8°C a couple of hours later. By 14 weeks of age temperature fell with sleep in a pattern like that described previously for babies aged 3–4 months with a minimum rectal temperature below 36·5°C. This pattern was maintained as babies got older.

Rectal temperature at bedtime was significantly higher in infants aged 6 weeks and older than in those under 6 weeks. By 12 weeks, the body temperature fell significantly further with sleep and produced the 'mature' rhythm.

There were noticeable individual differences in the age at which rectal temperature fell below 36·5 °C at some time during the night. Some babies achieved this at 6–8 weeks, others not until 14–16 weeks.

TEMPERATURE PATTERNS AND SLEEP

As we have presented the temperature data relative to the time of placing in a cot, the first hours always corresponded to a period of sleep. In the case of young babies, who slept as much during the day as the night, we recorded night time sleeps only, though we would perhaps expect similar results during the day. At older ages, the first part of the recording usually corresponded to the longest sleep period. We recorded the time between the baby being placed in his or her cot and the first time that the parents were disturbed. Figure 2 shows the mean duration of this sleep for babies of different ages compared with the minimum rectal temperature of those babies. As the mean sleep duration increased with age, the minimum nightly rectal temperature fell, though sleep duration increased substantially up to 8 weeks of age with little change in minimum rectal temperature. For individual babies, in the age range 6–16 weeks, however, there was a correlation between the minimum rectal temperature during the first sleep of the night, and the sleep duration (fig 3, r=0·464, product moment correlation p<0·01), suggesting that there was an association between temperature rhythms and sleep rhythms.

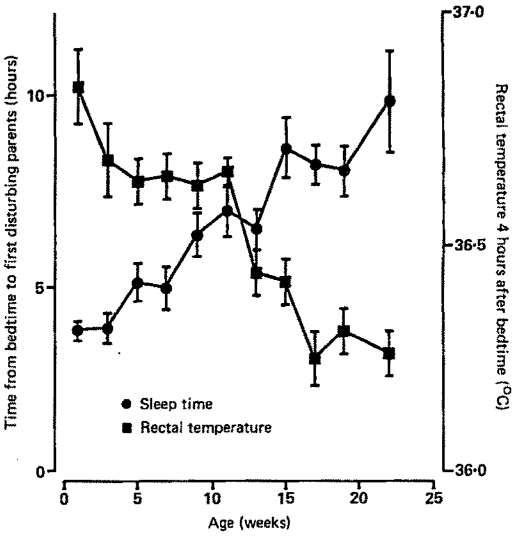

Figure 2 Association between rectal temperature in the middle of the night and age, compared with age related changes in the time from settling in the cot to first disturbance of parents.

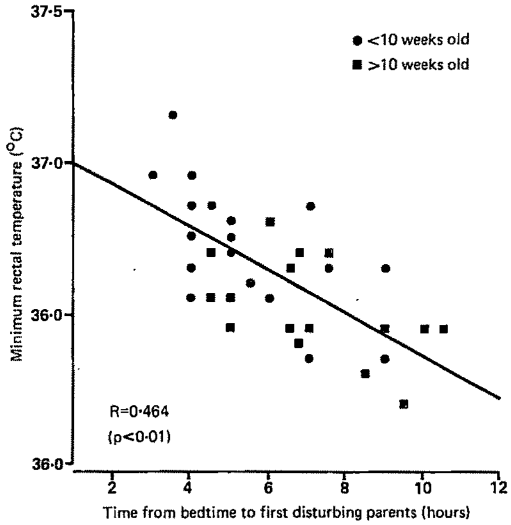

Figure 3 Association between time spent in the cot without disturbing parents and minimum rectal temperature at night for individual babies aged 6–14 weeks. Those whose rectal temperatures fall below 36·5°C at an earlier age also sleep for longer earlier.

Discussion

We have confirmed our previous observations that a predictable rhythm of night time rectal temperature develops by 16 weeks of age. The development occurs in stages. Babies aged 6 weeks have higher rectal temperatures than those aged 2 weeks at bedtime. Some weeks later rectal temperature falls more with sleep. There are considerable individual differences in the age at which a minimum rectal sleeping temperature develops, and these are associated with the appearance of longer night time sleeps.

Newborn infants, despite their known limited competence at thermoregulation,[5] maintain a relatively constant rectal temperature under hospital conditions, which is affected to only a small degree by feeding and sleeping.

Once babies sleep at home parents initially keep them well wrapped under rather warm conditions. By 4–6 weeks of age, however, the parents use a combination of room temperature and wrapping, which varies enormously from baby to baby, to maintain slightly cooler conditions; this is not changed for individual infants as they get older. There are effects of season on parental choice of wrapping and the room temperature but these are small and balanced out by the design of our study.

Despite constant conditions over the first few weeks of life waking rectal temperature, particularly at bedtime, is significantly higher at 6 weeks of age than at 2 weeks of age. This presumably reflects increased activity and increased effects of the feeds. Metabolic rate is known to increase at about this age.[6]

From 4–8 weeks of age sleeping is associated with a temperature fall to about 36·8°C, as happens during day time sleeps in older infants (and from our few observations at this age as well). By 12 weeks, however, night time sleeps are associated with a larger fall in temperature, and minimum rectal temperature stabilises at around 36·3°C by 18 weeks or so. This is a pattern similar to adults. Our data suggest that it continues over the rest of the first year of life, and presumably beyond. All the babies in our study have therefore developed a rhythm of night time temperature fall by 4 months of age. There do, however, appear to be substantial individual differences in the timing of the rhythm development, though the infrequency of our recording does not allow us to pinpoint them with confidence. We are now examining the age range 6–14 weeks in much more detail.

Many other circadian rhythms are developing at this time,[4] and in particular sleep patterns. There is an association, both on a population and individual basis, between increasing sleep duration and falling minimum rectal temperature. This is not caused by increasing time for cooling as the minimum rectal temperature is attained about the same time in sleeps of widely varying duration, also the temperature pattern is clearly regulated and is unaffected by environmental conditions. We cannot, of course, say whether lower rectal temperature predisposes infants to sleep longer, or rectal temperature falls lower, because the sleep pattern changes. It may just be that independent rhythms of temperature and sleep happen to mature at the same time. It is of interest, however, that the slow wave rapid eye movement sleep pattern changes at about the age that temperature rhythms stabilise.

It would be of considerable interest to correlate the development of temperature rhythm in individual babies with other circadian rhythms in heart rate and hormone secretion. Maybe in some infants there is a critical period around 3 months of age where some rhythms have developed and others have not so that physiological systems become less stable.

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Hypertension associated with increased renin concentrations in nephroblastoma

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Abstract

An infant with severe hypertension who had a nephroblastoma which was secreting active renin is described. Nephroblastoma must be included in the differential diagnosis of hypertension associated with increased renin concentrations, even in the absence of an abdominal mass.

Hypertension has been known to be associated with nephroblastoma since it was first reported in 1937 by Pincoffs and Bradley.[1] The incidence of hypertension has been reported as high as 60% in some series.[2] This was commonly thought to be due to catecholamine production. Recently, however, several cases of nephroblastoma have been reported with raised renin concentrations. This excess renin production may be from normal renal tissue as a consequence of distorted renal vasculature by tumour compression or it may be from the tumour itself. We report a case of nephroblastoma with severe hypertension with raised renin concentrations where tumour immunohistochemistry demonstrated perivascular renin containing cells.

Case report

A 10 month old boy presented with a two week history of malaise and anorexia. On examination he was irritable and flushed, and noted to be severely hypertensive with a blood pressure of 250/194 mm Hg. His pulse was 100/minute with no radial-femoral difference. A large irregular left sided abdominal mass was palpated. Biochemical analysis showed a sodium concentration of 131 mmol/l, potassium of 3·7 mmol/l, and urea of 9·5 mmol/l. An intravenous pyelogram and computed tomogram confirmed this mass to be arising from the left kidney. Hydroxymethyl mandelic acid and vanillyl mandelic acid markers for neuroblastoma were 16 and 24 µmol/mmol creatinine respectively (normal). Blood was also taken to measure renin concentrations.

Initial attempts at control of blood pressure with intravenous labetalol and hydralazine were unsuccessful, and so nine days after admission laparotomy was performed. Captopril, an acetyl coenzyme inhibitor, was given at induction with a good fall in blood pressure. A large nephroblastoma extending 5 cm down the ureter but with no macroscopic capsule invasion was removed. The right kidney felt normal.

Postoperatively the boy made a good recovery. His blood pressure fell to normal by the second postoperative day and his antihypertensive medication was stopped. The patient was given vincristine and actinomycin D (0·025 mg/kg of each) for 26 weeks according to the United Kingdom Children's Cancer Study Group protocol and is well one year postoperatively.

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Methods and results

RENIN ASSAY

Preoperatively and one week postoperatively, blood was taken for measurement of renin concentration. Active and total renin were measured by the method of Millar *et al.*[3] For active renin, 35 µl of plasma was incubated at 37°C in duplicate with excess ox renin substrate and antibody to angiotensin 1 at pH 6·9. The rate of generation of angiotensin 1 was measured by radioimmunoassay and the results calibrated against a preparation of international standard renin.[4] For total renin, the plasma was treated with trypsin in order to convert the prorenin to renin. At very high concentrations of renin, this can lead to a slightly low figure for total renin because of renin degradation by trypsin and problems with the dilutional technique. Inactive renin was calculated as total renin-active renin.

Total renin and particularly active renin concentrations were found to be grossly raised preoperatively at 13 385 µU/ml and 9 674 µU/ml respectively (normal 50 µU/ml and 200 µU/ml). Postoperatively these fell to 8 and 55 µU/ml.

HISTOLOGY

The specimen weighed 635 g and measured 17× 10×9 cm. The tumour was a moderately well differentiated nephroblastoma predominantly blastemal in type but with prominent glomeruloid structures and some areas of increased tubular differentiation, and was classified as stage 2 favourable histology.

Using an antibody to pure renin and a peroxidase-antiperoxidase technique,[5] most of the cells containing immunoreactive renin were present in a perivascular position in the blastemal areas as previously described.[5] Within the glomeruloid structures there were some renin containing cells in a mesangial distribution. These cells contained granules that stained positively for renin and their appearance suggested that they were renin secreting cells.

Discussion

In the case reported, active renin was raised 50-fold preoperatively and fell postoperatively to

Cases of nephroblastoma associated with hypertension and raised renin concentration

Author	*Age*	*Sex*	*Side (R, right; L, left)*	*Blood pressure (mm Hg)*	*Renin concentration (µU/ml)*	
					Preoperative	*Postoperative*
Spergel *et al*[6]	5 months	F	R	210/160	14·5	2·8
Mitchell *et al*[7]	23 months	F	R	260/200	12·3	0·66
Marosvari *et al*[8]	18 months	M	L	160/120	15·0	7·0
Sukarochano *et al*[2]	4·5 years	M	L	200/110	16 000*	220*
Sukarochano *et al*[2]	5 years	M	R	162/128	810	
Ganguly *et al*[9]	4 years	M	R	200/140	10·1	0·09
Cobb and Vaughan[10]	27 months	M	R	210/140	Raised	ND
Sheth *et al*[11]	16 months	M	R	200/120	39·5	1·6
Luciani *et al*[12]	3 years	M	L	200/120	51·0	1·1
Luciani *et al*[12]	4 years	M	L	210/140	3·4	0·47
Spahr *et al*[13]	4 years	M	L	170/120	8·8	0·35
Stine *et al*[14]	9 months	M	L+R	162/110	51·9	0·77
Suthers *et al*[15]	2 years	M	L	220/148	5·2	0·33
Yokomori *et al*[16]	9 months	F	L+R	140/90	99·0	0·05
Khan *et al* (current case)	10 months	M	L	250/194	268	0·16

*No normal values stated, units are ng. ND, not done.

within normal limits as did the blood pressure. The inactive form was also raised but not to the same degree. The renin was found to be arising from the tumour.

The first association of nephroblastoma with raised serum renin concentrations was in 1969.[6] The case reported was a 5·5 month old child with a blood pressure of 210/160 mm Hg associated with hypokalaemia, abnormal glucose tolerance, and increased renin concentrations. Mitchell *et al* demonstrated raised renin concentrations in tumour tissue as well as serum in a 23 month old child with hypokalaemia and a blood pressure of 260/200 mm Hg.[7] This was thought to be evidence of abnormal renin production from the tumour rather than as a result of an ischaemic stimulus to the renin angiotensin system in the rest of the kidney. Since that report of Mitchell *et al* there have been 12 other reports of nephroblastoma associated with hypertension and increased renin concentrations (table). There is a sex ratio of four males to one female and the average age is 3 years. The time taken for the blood pressure to fall in most cases was between one and three weeks after nephrectomy. This time appears unrelated to the presence or subsequent development of metastases.

There have been a number of cases of nephroblastoma with increased concentrations of renin who were normotensive. Renin production was looked at in eight children with nephroblastoma by Voute *et al.*[17] Blood pressure was normal in all eight while the serum renin concentration was found to be raised. In the five studied postoperatively, there was noted to be a fall in serum renin after nephrectomy. Day *et al* found renin in tissue from nephroblastoma with a much greater molecular weight than normal plasma and kidney renin.[18] They suggested the existence of an inactive prohormone and this inactive form of renin could account for the large number of cases of nephroblastoma which are not associated with hypertension. Carachi *et al* looked prospectively at eight children with nephroblastoma measuring both active and inactive renin.[19] In seven of these cases there was found to be a raised concentration of serum renin. However, this increased amount was seen to comprise mainly the inactive form. Only one child was hypertensive.

Nephroblastoma should always be considered as part of the differential diagnosis for hypertension in the young. Renin concentrations should be checked and if found to be raised, a careful search should be made for a nephroblastoma even in the absence of an abdominal mass—particularly where there is no evidence of renal parenchymal disease.

We would like to thank Mr AHB Fyfe for permission to present this case. Thanks also to the departments of pathology, radiology, and medical illustration in the Royal Hospital for Sick Children, Glasgow.

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Treatment of hyperkalaemia with intravenous salbutamol

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Abstract

Thirteen children with hyperkalaemia were treated by intravenous infusions of salbutamol, 4 μg/kg over 20 minutes. Reductions in the mean (SD) plasma potassium concentrations, of 1·48 (0·5) and 1·64 (0·5) mmol/l were obtained at 40 and 120 minutes, respectively, after completion of the infusions. No side effects were noted.

Hyperkalaemia is conventionally defined as a plasma potassium concentration of greater than 5·5 mmol/l in children and adults and 6·0 mmol/l in the newborn. Because of its potentially lethal consequences, usually cardiac arrhythmias culminating in asystole, hyperkalaemia is a medical emergency demanding urgent treatment. Treatment should be rapid, predictable, and if possible have a sustained effect. Nebulised salbutamol has been reported to cause a fall in the plasma potassium concentration,[1] and was once the recognised treatment for hyperkalaemic familial periodic paralysis.[2] Salbutamol given intravenously has recently been shown to be effective in treating hyperkalaemia in adults with end stage renal failure.[3] We report our experience with the use of intravenous infusions of salbutamol in 13 children with hyperkalaemia.

Patients and methods

Between July 1988 and December 1989, 13 children with hyperkalaemia were treated with salbutamol by intravenous infusion to try and reduce their plasma potassium concentrations. Six infants had hyperkalaemia as a result of acute renal failure after cardiac surgery, and the remaining seven had a variety of renal disorders that culminated in hyperkalaemia (table).

All the children were anuric at the time that the salbutamol was given. None of the children with acute renal failure were receiving adrenaline but all were on low doses of dopamine 3 μg/kg/minute and dobutamine, median dose 10 μg/kg/minute. Before the infusion of salbutamol all patients received 10% calcium gluconate (0·5 ml/kg) as an intravenous infusion over five minutes with electrocardiographic monitoring to try and minimise the potential cardiotoxic effects of potassium.

Salbutamol was given in a dose of 4 μg/kg made up in 5 ml water for injection and infused at a constant rate over 20 minutes with electrocardiographic monitoring. No tachyarrhythmias or other complications occurred.

The six infants with acute renal failure after cardiac surgery had a mean age of 0·24 years (range 0·01–0·5), a mean weight of 4·0 kg (range 3·2–5·5), a mean serum creatinine concentration of 193 μmol/l (range 150–254), and a mean (SD) initial plasma potassium concentration of 6·7 (0·14) mmol/l before treatment. The initial mean plasma potassium concentration of the group with underlying renal disease and hyperkalaemia (n=7) was 6·7 (0·34) mmol/l. The mean age, weight, and plasma creatinine concentration of this group were 6·1 years

Details of patients studied

Case No	*Sex*	*Age (years)*	*Creatinine concentration (μmol/l)*	*Initial potassium concentration (mmol/l)*	*Diagnosis*	*Final management*
Children with acute renal failure:						
1	F	0·42	254	6·7	Acute renal failure, transposition great arteries	Dialysis
2	F	0·25	180	6·8	Acute renal failure, anomalous left coronary artery	Support
3	M	0·50	170	6·7	Acute renal failure, transposition great arteries	Support
4	F	0·17	220	6·9	Acute renal failure, atrioventricular septal defect	Dialysis
5	F	0·10	150	6·5	Acute renal failure, aortic coarctation	Dialysis
6	M	0·01	190	6·7	Acute renal failure, mitral atresia	Support
Mean (range) of cases 1–6		0·24 (0·01–0·5)	193 (150–254)	6·7 (6·5–6·9)		
Children with chronic renal failure:						
7	M	2·5	330	6·9	Rejection of renal transplant	Dialysis
8	M	1·0	675	6·9	Rejection of renal transplant	Dialysis
9	M	1·1	356	6·7	Rejection of renal transplant	Dialysis
10	M	10·0	620	6·6	End stage renal failure/reflux nephropathy	Dialysis
11	F	16·7	528	6·8	Rejection of renal transplant	Dialysis
12	F	8·0	365	7·0	Rejection of renal transplant	Dialysis
13	M	4·0	414	6·0	End stage renal failure, nephronophthisis	Dialysis
Mean (range) of cases 7–13		6·2 (1·0–16·7)	470 (330–675)	6·7 (6·0–7·0)		

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(range 1·0–16·7), 17·0 kg (range 5·9–39·3), and 470 μmol/l (range 330–675), respectively, at the time of treatment.

The plasma potassium concentration was measured with an ion selective electrode (Hitachi 737). One millilitre of blood was withdrawn, placed in a lithium heparin tube, and sent immediately for analysis. In those patients with indwelling arterial lines, arterial blood was sampled. In the remainder venous blood was obtained by repeat venepuncture, care being taken to avoid haemolysis. Potassium was estimated consistently in either arterial or venous blood in each individual patient. Further measurements of the plasma potassium concentration were made at roughly 40 and 120 minutes after the salbutamol infusion had ceased in 13 and nine patients, respectively. Four children were excluded from further study at 120 minutes, three because peritoneal dialysis had been started and one because a Tenckhoff peritoneal catheter was being inserted.

Statistical analysis was by paired Student's *t* test and a p<0·05 was accepted as significant. The results are expressed as mean (SD).

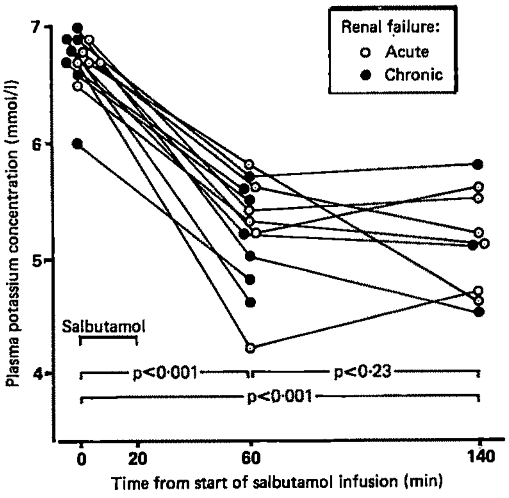
Results

The changes in the plasma potassium concentration with time after intravenous salbutamol infusion are shown in the figure. The mean (SD) reduction in plasma potassium concentration was 1·48 (0·5) mmol/l (n=13, p<0·001) and 1·64 (0·5) mmol/l, (n=9, p<0·001) at 40 and 120 minutes, respectively, in the whole group after completion of the salbutamol infusion.

Changes were similar in the two subgroups of patients at both 40 and 120 minutes (figure). In those children who developed acute renal failure after cardiac surgery the salbutamol infusion resulted in no significant change in heart rate (135 (10) beats/minute before infusion compared with 139 (8) during infusion), mean arterial pressure (70 (5) mmHg compared with 68 (4)), or arterial oxygen saturation (92 (4)% compared with 90 (3)%), nor was there a need to increase the inotropic support during the period of the study.

Discussion

The definitive treatment of hyperkalaemia in renal failure is to remove the excess potassium by dialysis, supplemented if necessary by ion exchange resins. It is often necessary, however, to 'buy time' for these treatments to work by inducing a shift of potassium from the extracellular to the intracellular space. This can be achieved by the intravenous administration of sodium bicarbonate, or dextrose and insulin, and β adrenergic stimulation also lowers the extracellular potassium concentration in this way.[4, 5]



Plasma potassium concentrations at the start of infusion of intravenous salbutamol and at 60 and 140 minutes later in children with acute and chronic renal failure.

Recent work, however, has suggested that bicarbonate alone is slow and limited in effect,[6] and there is a high incidence of hypoglycaemia associated with the use of dextrose and insulin causing some physicians to advocate the use of dextrose alone.[6]

β_2 Adrenergic stimulation is known to promote extrarenal potassium uptake[4]: we have used intravenous salbutamol, a β_2 agonist to produce this effect. Salbutamol acts by binding to the β_2 adrenergic receptors in the liver and muscle cell membranes. This then stimulates the enzyme adenylate cyclase, which increases the conversion of ATP to 3'5' cyclic AMP. This in turn acts on the sodium/potassium ATPase pump and facilities intracellular potassium uptake.[4]

Stemmer *et al* found that nebulised salbutamol was ineffective in promoting extrarenal potassium uptake in patients with end stage renal failure,[5] but we found that an intravenous infusion of salbutamol was as effective in patients with acute on chronic renal failure as in those with acute renal failure after cardiac surgery despite the different ages and different degrees of severity of renal failure within the two groups.

Lens *et al* have recently shown that salbutamol given intravenously was as effective as dextrose and insulin in producing a reduction in the plasma potassium concentration in patients with chronic renal failure and it had no side effects: they also showed the effects of salbutamol given intravenously and of dextrose and insulin were additive.[3]

We have shown that hyperkalaemia can effectively be reduced by one intravenous dose of salbutamol (4 μg/kg) given at a constant rate over 20 minutes. The effect lasts for at least 120 minutes after the end of the infusion allowing time for dialysis to be instituted if appropriate. The treatment is safe and avoids the risk of the hypoglycaemia that is caused by the use of dextrose and insulin in infants and small children. We now recommend salbutamol infusion as the first treatment of choice in children with dangerous hyperkalaemia; it can be combined with bicarbonate, ion exchange resins, and dextrose and insulin if necessary.

We thank the following for their permission to report their patients: Professor MJ Tynan, Professor C Chantler, Dr EJ Baker, Dr SA Qureshi, and Dr SPA Rigden.

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Nesidioblastosis: evidence for autosomal recessive inheritance

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Abstract

The risk of recurrence of nesidioblastosis is unclear. Thirty patients from 28 families were studied; the marriages were consanguineous in five families. The ratio of subsequent affected to unaffected siblings was similar to that of an autosomal recessive condition and the sex ratio was close to 1.

Nesidioblastosis is a well recognised cause of hypoglycaemia in infancy. Most cases appear sporadic but several familial cases have been reported and the recurrence risk remains uncertain. We have seen two additional families each with two affected siblings; this prompted a review of all patients treated at this hospital.

Patients and methods

Children with nesidioblastosis were identified from the inpatient hospital register. Children with Beckwith-Wiedemann syndrome and those born to diabetic mothers were excluded. The minimum criteria for diagnosis included recurrent episodes of hypoglycaemia (blood glucose concentration <2·2 mmol/l) associated with simultaneously inappropriately raised plasma insulin concentrations (plasma insulin >7 mU/l (>50 pmol/l)). In all children who underwent subtotal pancreatectomy there was also histological confirmation of the diagnosis. Where possible the family history was also checked directly with the parents.

Results

A total of 30 patients were identified from 28 families. The sex ratio was close to 1 (16 boys: 14 girls, figure). Eighteen of the children were white, four Asian, seven Arabic, and one was of mixed parentage. Consanguinity was present in five (18%) of the families and in both families with more than one affected child. Altogether 21 of the children underwent subtotal pancreatectomy and the others have been managed medically.

Only six of the 21 families for whom up to date information was available have had further children. Of the 10 subsequent born children eight were normal (80%) and two affected (20%). These results are similar to those expected (75%:25%) for an autosomal recessive condition. The family of patient 28 also had an elder daughter (second born child) in whom a diagnosis of nesidioblastosis was highly probable but could not be proved. Had this child also been included as an index case the ratio of subsequent normal to affected children would have been 73%:27%.

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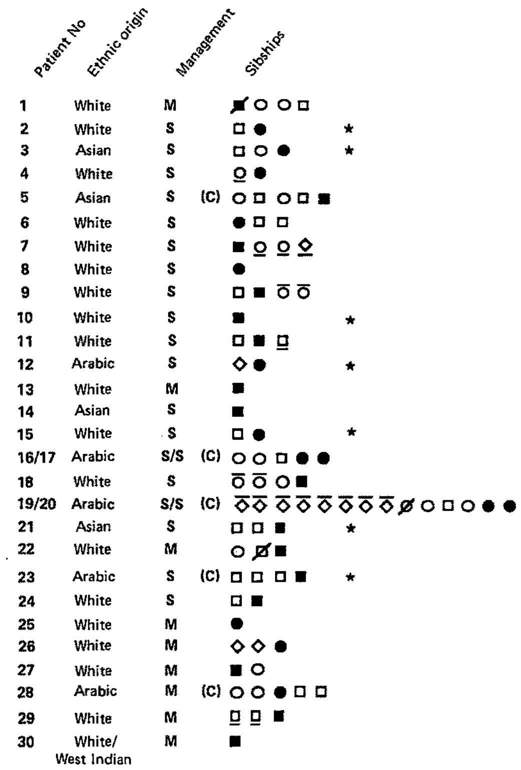

*Family pedigrees of children with nesidioblastosis. Boys shown as squares, girls as circles, sex unknown as diamonds. Affected children shown as closed symbols. Paternal half siblings denoted by a superscript line above symbol, maternal half siblings denoted by a subscript line underneath symbol. M denotes medical management, S denotes surgical management (subtotal pancreatectomy), (C) denotes parental consanguinity, and * denotes up to date information not available. Children who have died are shown by a line through the symbol.*

Discussion

Familial nesidioblastosis has been described as an autosomal recessive condition,[1] but the majority of cases reported appear to have been sporadic. The first well documented familial cases were two siblings described in 1976,[2] although a probable case was reported in 1970.[3] Since then we are aware of only five further reports of familial nesidioblastosis (cited by Moreno *et al*[4]) and in only one family described was there parental consanguinity.

We describe four further definite familial cases of nesidioblastosis occurring in two different families. This probably under represents the real frequency of familial cases in this series as the family of patient 28 had an elder daughter who presented in early infancy with recurrent hypoglycaemic convulsions. This child in whom a diagnosis of nesidioblastosis is probable was managed abroad and full documentation was not available.

In support of an autosomal recessive inheritance pattern we have observed a sex ratio close to 1. Five cousin marriages are reported; however, it should be noted that these marriages are confined to ethnic groups with a high prevalence of consanguinity. For the 21 families in whom complete up to date information was available the ratio of subsequently affected offspring to normal children after an initial affected child was 1:4. If the probable case from the family of patient 28 was included the ratio would be 1:2·7 (expected ratio for an autosomal recessive condition 1:3).

Although the suggestion of autosomal recessive inheritance was made several years ago the question remains unresolved, possibly because parents limited the size of their families. In this series only six of the 21 families, for whom up to date information was available, have subsequently gone on to have further children. This may partly reflect the influence of an affected child on parental plans for further offspring which is not surprising as there is a high rate of mental retardation in survivors.

In conclusion paediatricians and geneticists should be aware that nesidioblastosis can be familial and is probably autosomal recessive. This is important both for genetic counselling and to enable a prompt diagnosis to be made in any subsequent affected sibling as delay in the institution of appropriate treatment may adversely affect outcome. Any further understanding of the genetic mechanisms in familial nesidioblastosis must await the recognition of a chromosomal or genetic marker.

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Increasing incidence of hypertrophic pyloric stenosis

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Abstract

The incidence of pyloric stenosis in the Mersey region rose from 1·54/1000 births in 1976–8 to 2·22/1000 births in 1986–8. Reliance on ultrasonography for diagnosis in the 1980s resulted in fewer 'tumours' being felt; diagnostic delay was not shortened overall but serial ultrasonography showed evolving lesions in six patients. Clinical examination and selective use of ultrasonography is advocated.

An increase in the incidence of infantile hypertrophic pyloric stenosis was observed in several parts of this country in the late 1970s,[1–3] but it is not known if this trend was maintained in the 1980s. The introduction of ultrasonography and its subsequent widespread acceptance for the diagnosis of pyloric stenosis has brought changes in clinical practice in the 1980s, but these changes have not been quantified.[4] We studied two cohorts of patients with pyloric stenosis in the Mersey region with a 10 year period separating them to identifying changes in the incidence and pattern of diagnosis.

Patients and methods

We conducted a retrospective survey of all patients with a confirmed diagnosis of infantile hypertrophic pyloric stenosis in the Liverpool and South Sefton areas of the Mersey region for the periods 1 April 1976–31 March 1978 and 1 April 1986–31 March 1988. Patients with pyloric stenosis in this region were all treated in the Royal Liverpool Children's Hospital; they were identified from the Hospital Activity Analysis data as well as the operating theatre records, and their hospital records were studied. Patients with pyloric stenosis referred to this hospital from other regions were excluded. Information on the birth rates in areas of the region during the study periods was obtained from Mersey Regional Health Authority.

Ultrasonography was not available in 1976–8, unlike 1986–8. There was no strict policy for referral for scanning, 72% of the patients being scanned, incuding most patients without a palpable 'tumour' and about half in whom the lesion was palpable.

The χ^2 test was used for assessment of the significance of differences between groups, and a p value of $<0·05$ was accepted as significant.

Results

The number of patients with pyloric stenosis, the incidence/1000 live births, the male:female ratio, the time from the onset of symptoms to hospital admission, the time from hospital admission to diagnosis and the number of palpable lesions recorded during the study periods are shown in the table. In addition, during the

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Patients with pyloric stenosis between April 1976–March 1978 and April 1986–March 1988 in the Mersey region

	1976–78 (n=91)	*1986–88 (n=146)*	*p Value*
Incidence/1000 live births	1·54	2·22	<0·01
Male:female ratio	3·55:1	8·35:1	<0·05
Mean (SD) time from onset of symptom to admission (days)	8·6 (9)	9·6 (10)	0·2
Mean (SD) time from admission to diagnosis (days)	0·9 (1·2)	0·8 (1·1)	0·5
Percentage that were palpable	91	64	<0·001

period 1986–8 there were six patients who had normal or equivocal initial ultrasonographic examinations but repeat scans after one to four days because of persistence of symptoms showed the typical features of pyloric stenosis. Two other patients had initial normal ultrasonographic scans but did not have repeat examinations; instead the diagnosis of pyloric stenosis was made by contrast studies. In the same period there were two patients who had a preoperative diagnosis of pyloric stenosis but at operation were found not to have a pyloric 'tumour'; the preoperative diagnosis had been made by clinical examination (palpable lesion) in one and by ultrasonography in the other.

Discussion

An increase in the incidence of infantile hypertrophic pyloric stenosis was recorded in central Scotland,[1] the West Midlands,[2] and South Glamorgan[3] in the late 1970s. No change in the incidence of the condition was observed in western Australia between 1971 and 1984.[5] Our figures suggest that there was a small increase in the incidence of pyloric stenosis in the Mersey region during the late 1980s compared with the 1970s. Our incidences of 1·54/1000 births in 1976–8 and 2·22/1000 births in 1986–8 were, however, low compared with the figures from Scotland, West Midlands and South Glamorgan (3·5–8·8/1000 births),[1-3] and corresponded to those from Australia.[5] Yearly incidences of pyloric stenosis are known to fluctuate and the modest increase in incidence seen during the second period of our series may simply be part of this phenomenon. It has also been suggested that increased awareness of the condition may lead to hospital referral of mild cases that might otherwise have been managed conservatively in the community.[6] The referral time in our series has remained unchanged in the past decade and gives little cause for such optimism. We have no explanation of the increased male preponderance in recent years in our series. The male:female ratio increased in the West Midlands[2] and decreased in South Glamorgan[3] in the late 1970s.

Our two study periods were separated by a decade during which ultrasonography was introduced and became easily available in our hospital. Has this practice led to earlier diagnosis? Overall, there was a significant change in the duration from hospital admission to diagnosis in the two periods in our series. The rate of palpable lesions dropped significantly during the second period of study. The most likely explanation is that clinicians are becoming over-reliant on ultrasonography for diagnosis, with the risk that the skill and the motivation to 'feel for a pyloric tumour' are gradually being lost. Occasionally, particularly in some early cases of pyloric stenosis, ultrasonography may give a false negative diagnosis, but as the 'tumour' evolves, repeat ultrasonography often allows the diagnosis to be made. With both physical examination and ultrasonography there is also a small risk of false positive diagnosis. The high degree of sensitivity and selectivity of ultrasonography in the diagnosis of pyloric stenosis, however, should not be allowed to become an excuse for clinical complacency. Detection of a palpable lesion requires skill and patience. Clinicians should re-emphasise these virtues and aim to diagnose most cases of pyloric stenosis by clinical examination alone. Investigations, of which ultrasonography should be the first choice, will then be required only in selected circumstances.

We thank the Mersey Regional Health Authority for helping us to collect our data, and our clinical and radiological colleagues for allowing us to study their patients.

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High mebendazole doses in pulmonary and hepatic hydatid disease

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Abstract

Thirty nine children with 71 hydatid cysts were given mebendazole orally in a dose of 100–200 mg/kg/day for 12 weeks and were followed up for a mean (SD) of 63 (24) months. Twenty children (three of them after a second course) were cured and another two avoided at least one operation. No serious side effects of the drug were observed.

Experience during the last 10 years with several benzimidazole derivatives, mainly mebendazole and albendazole, suggests that chemotherapy may, in certain circumstances, replace surgery in the treatment of hydatidosis in children.[1 2] In this study the effectiveness of mebendazole has been evaluated prospectively.

Patients, methods, and results

Thirty nine children (17 boys and 22 girls) aged 2–14 years (mean age 7·5 years) with cystic hydatidosis received mebendazole orally for 12 weeks (100–200 mg/kg/day with a maximum daily dose of 6 g) in divided doses with meals. Nine patients who failed to respond received a second course of treatment after an interval of three to six months. The 39 patients had 71 cysts: 33 in the lungs (seven of which had ruptured), 37 in the liver, and one in the spleen. The patients were followed up during the treatment to observe any haematological, hepatic, renal, visual, and hearing problems because of toxicity.

The results of the treatment were evaluated according to the organ involved by radiography, computed tomography, or ultrasonography, and were classified into cure (disappearance of the cysts), improvement (decreased size of the cyst and/or calcification or various alterations in density and/or negative viability test), and failure.

The results are summarised in the table. The mean (SD) follow up period for the successfully treated cysts was 63 (24) months. The successfully treated lung cysts were smaller (mean (SD) diameter 5·24 (1·92) cm) than those which persisted (7·94 (4·38) cm, $p<0{\cdot}05$). Similar differences were also found in the hepatic cysts (3·93 (1·87) and 7·78 (3·08) cm, respectively, $p<0{\cdot}001$).

*Results of the mebendazole treatment (n=70)**

	Lungs	*Liver*
No of cysts	33	37
Cure (%)	22 (67)	10 (27)
Improvement (%)	2 (6)	11 (30)
Failure (%)	9 (27)	16 (43)

*There was one cyst found in the spleen, which did not respond to treatment.

Of the 39 patients 20 (three of them after a second course) were cured and two with multiple cysts avoided at least one operation. Nine of the 20 cured patients had multiple cysts in one or more organs.

The mean (SD) plasma mebendazole concentration two hours after the morning dose was 116 (47) ng/ml. Serious side effects from mebendazole were not observed. Seven children had a low grade fever, two children had gastric discomfort, and two others had a transient moderate rise of transaminase activity.

Discussion

Mebendazole, a synthetic benzimidazole derivative, is effective against the larval stages of *Echinococcus granulosus* and *E multilocularis*. It kills the parasite by limiting its glucose uptake through the disruption of the microtubles in the germinal membrane cells of hydatid cysts.[3]

During the last decade, mebendazole has been on clinical trial, especially in adults, as a non-surgical treatment of human hydatid disease.[1 4] As far as we know this is the largest series in children with the longest follow up period.

The effects of mebendazole treatment in the literature are not constant. Several factors including drug dose, duration of treatment, age of the patients, size and location of the cysts, and duration of follow up may be responsible for this controversy.[1 4] The results of this study are considered as favourable, because about two thirds of the pulmonary and one third of the hepatic cysts disappeared without any relapse.

The high effectiveness of mebendazole in this study could be attributed to the higher doses of the drug used and/or the younger age of the patients. In our first published paper we successfully used a dose of 100 mg/kg/day in only two patients.[5] The absence of serious side effects of mebendazole enabled us to use a dose of 100–200 mg/kg/day for the 39 cases of the present series. With the above dose of mebendazole we achieved therapeutic plasma concentrations (100 ng/ml), although they were measured two hours after the morning dose instead of four.[6] On the other hand, it is known that the efficacy of mebendazole is better in young age.[4] The assumption is that younger patients tend to have rather smaller and younger cysts. Furthermore in our study, as in others,[4] the efficacy of the drug was correlated with the size of the cysts. Cysts with a diameter of 4–5 cm responded better to treatment. The common

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denominator of the age of the patient and the size of the cyst is probably the thickness of cystic adventitia, which is the barrier mebendazole should penetrate in order to reach the germinal layer. The cyst's adventitia is a local reaction of host tissue and pulmonary adventitias are thinner than those of liver cyts.[4] This could explain the better results in the treatment of pulmonary cysts obtained by us and others.[1]

We have therefore been able to show in this study that high doses of mebendazole have been effective against hydatidosis of children especially in cysts of medium and small size, without serious side effects, and can be used as an alternative treatment.

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Familial growth hormone releasing factor deficiency in pseudopseudohypoparathyroidism

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Abstract

A mother with pseudopseudohypoparathyroidism and her short son showed poor spontaneous growth hormone secretion, and provocation tests suggested a deficiency of growth hormone releasing factor. This is the first report of growth hormone releasing factor deficiency in pseudopseudohypoparathyroidism. The boy has responded well to growth hormone treatment over a period of three years.

Case reports

A 4·5 year old healthy boy presented with short stature (height standard deviation score (SDS) −3·93). His mother was short (145·2 cm) and had clinical features of pseudopseudohypoparathyroidism (short fourth and fifth metacarpals and metatarsals, round facies). She was euthyroid but in the past had been treated with carbimazole and radioactive iodine for hyperthyroidism. The child had normal thyroid function. Both the boy and his mother were normocalcaemic with normal plasma cyclic AMP responses to parathyroid hormone stimulation.

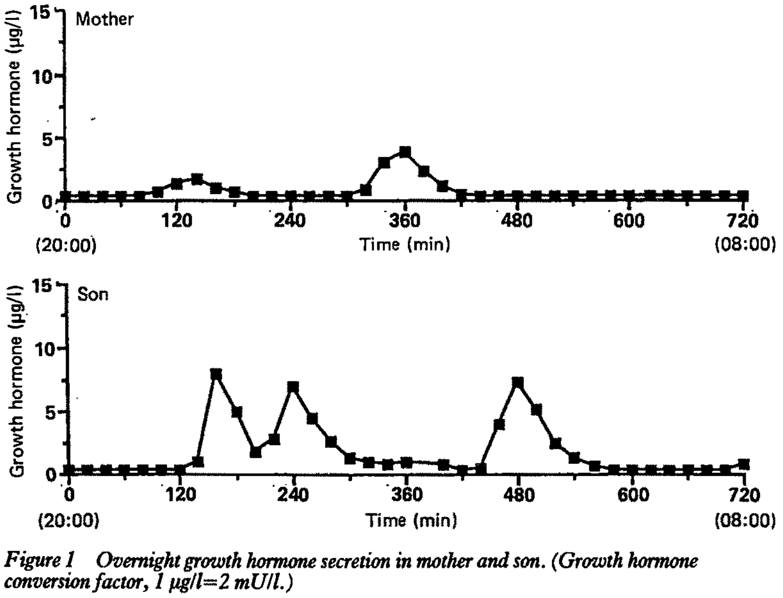

Figure 1 Overnight growth hormone secretion in mother and son. (Growth hormone conversion factor, 1 μg/l=2 mU/l.)

Both mother and son had poor spontaneous overnight growth hormone secretion (fig 1). One would have expected three to four pulses of growth hormone during the night with pulse amplitude >10 μg/l in the child. The mother failed to produce any significant growth hormone pulses. The boy's response to insulin induced hypoglycaemia was poor with a peak growth hormone concentration of 4·1 μg/l. The cortisol response was satisfactory. However when given growth hormone releasing factor both mother and child showed a very pronounced response: the child with a peak growth hormone concentration of >95 μg/l and the mother with a concentration of 73 μg/l.

Since the age of 5·7 years the boy has been treated with growth hormone (24 IU/m^2/week). His height SDS at the start of growth hormone treatment was −3·70 with a height velocity of 4·9 cm/year (height velocity SDS −1·47). Height velocity over the first year of treatment increased to 9·1 cm/year (height velocity SDS +3·28). Good growth has been maintained on growth hormone for three years and he now has a height SDS −1·95 (fig 2). Bone age has not advanced abnormally and his final height prognosis has improved.

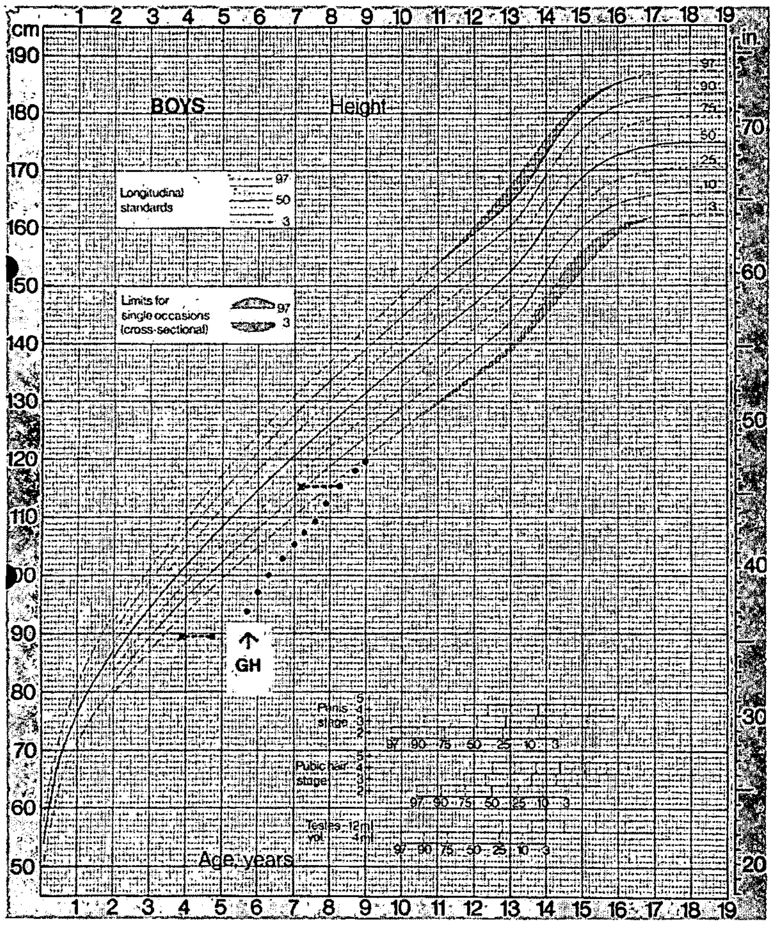

Figure 2 Growth chart of boy.

Discussion

This case illustrates the importance of examining the parents of a child presenting with short stature. The diagnosis in this family was apparent by examination of the mother, who had characteristic dysmorphic features.

The classical form of pseudohypoparathyroidism (type 1a) is characterised by certain features including round face, short stature, shortened metacarpals and metatarsals, subcutaneous calcification, and calcium deposits in the basal ganglia. These patients have a raised serum phosphorus, hypocalcaemia, and high endogenous concentrations of parathyroid hormone with blunted response to exogenous parathyroid hormone. Individuals with similar physical characteristics, but normal biochemistry, are described as having pseudopseudohypoparathyroidism. It is likely that the two conditions are not distinct and could be variable expressions of one entity. Both conditions may be found in the same family and the individual's biochemical state can change so that nomocalcaemic individuals can become hypocalcaemic and vice versa. The phenotype is highly variable as patients with classical biochemistry may have no dysmorphic features and may be of normal or above average height, the age and mode of presentation is unpredictable, and many patients are missed in early childhood.[1] The dysmorphic features are not apparent at birth but evolve through childhood as the skeleton matures. The classical short metacarpals and metatarsals may not appear until mid-childhood or even adolescence. Thus pseudohypoparathyroidism / pseudopseudohypoparathyroidism cannot be excluded by the absence of dysmorphic features in childhood. The condition is probably autosomal dominant, so first degree relatives of known patients require careful observation. Short stature or poor height velocity may be the first indication that a child is affected.

Abnormalities of secretion of other peptide hormones, particularly thyroid and gonadotrophins, have been described in patients with pseudohypoparathyroidism,[2 3] and it is reasonable to postulate that abnormalities of growth hormone secretion may also occur. One patient with absent growth hormone response to arginine provocation has been described.[4] It is likely that there is considerable variation in growth hormone secretion as patients with pseudohypoparathyroidism can be of normal size.

Several mechanisms could be involved in the short stature of patients with pseudohypoparathyroidism. There could be defects in both growth hormone and/or growth hormone releasing factor secretion. The growth hormone releasing factor receptor protein on the somatotroph activates a coupling protein to stimulate adenylate cyclase activity and hence growth hormone synthesis and release. In pseudohypoparathyroidism the basic defect causing resistance to parathyroid hormone may be a deficiency in the guanine nucleotide regulatory protein or receptor-cyclase coupling protein. Thus in some patients with pseudohypoparathyroidism the growth hormone secretory defect may be in receptor binding for the releasing factor and/or activation of its regulatory protein, similar to that postulated for the defect in parathyroid hormone regulatory protein.[5] In the family described here, however, the abnormality demonstrated is in the growth hormone releasing factor secretion rather than in its binding to the somatotroph.

This mother and child showed poor spontaneous nocturnal growth hormone secretion, with the child having an inadequate response to insulin induced hypoglycaemia. The fact that both have supramaximal responses to growth hormone releasing factor suggests that they have functioning somatotrophs, and that their defect is in the production or secretion of growth hormone releasing factor. This would lead to functional growth hormone deficiency and is likely to be the cause of the short stature in these patients. The boy has been treated successfully with growth hormone with improvement in his height prognosis. This is the first report of growth hormone releasing factor deficiency in pseudopseudohypoparathyroidism.

In conclusion—many adults and children with pseudohypoparathyroidism / pseudopseudohypoparathyroidism are conspicuously short. One should not assume that this is just part of the syndrome, as they may have an associated abnormality of growth hormone secretion. It is possible that the short stature of pseudohypoparathyroidism / pseudopseudohypoparathyroidism may be treatable with growth hormone and adult height improved.

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4 Shima M, Nose O, Shimizu K, *et al.* Multiple associated endocrine abnormalities in a patient with pseudohypoparathyroidism type la. *Eur J Pediatr* 1988;147:536–8.

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Suffocation

Most of us have difficulty comprehending the full repertoire of human behaviour in apparently sane people and therefore most kinds of child abuse initially arouse feelings of disbelief. Deliberate suffocation of children by parents is one such but that it occurs there can be no doubt because to the best of my knowledge it is the only form of child abuse (other than ritual or pornographic abuse) which has been recorded on videotape.[1] Roy Meadow (*J Pediatr* 1990;**117**:351–7) has recently presented information about 27 children, each from a different family, who were abused in this way. Nine of the children died and one had severe cerebral injury. In at least 11 cases the mother was either filmed or observed suffocating the child and in the others she either confessed or was found guilty in the criminal court. The families lived in different parts of Britain and came to Professor Meadow's attention because of his widely known interest in this problem and from clinical, social work, and legal sources. Twenty four children had had previous episodes of apnoea, cyanosis, or seizures and half of those had had more than 10 such episodes. Their ages at the time of the first episode ranged from 2 weeks to 18 months and on discovery of the suffocation, from 2 to 48 months. There were 33 older siblings of whom 18 had died suddenly and unexpectedly. At necropsy 13 of these deaths had been certified as SIDS. In all 27 known cases of suffocation the mother was the perpetrator, although it is known that occasionally the father may do it. Not all of the reported episodes in the suffocated children were due to suffocation, some were fabricated reports. Some of the mothers later described feelings of hatred for the child giving as reasons the apparent contrast between their own misery and the child's happiness, or the fact that the child resembled his father, or interfered with social life or work.

The baby who presents to hospital with a history of apnoea is one of the most worrying problems in paediatrics. Most are found to be well and are sent home with or without an apnoea monitor and with such additional support to the parents as seems appropriate or feasible but inevitably some later die suddenly and we are left wondering 'could we have done more?' In most cases probably we couldn't but we must be alert to the possibility of suffocation and prepared to act in the interests of the child if the possibility seems substantial. As with all child abuse it is impossible always to run an exact course between on the one hand putting the child at risk and on the other causing suspicion to fall on innocent parents.

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[1] Southall DP, Stebbens VA, Rees SV, *et al.* Apnoeic episodes induced by smothering: two cases identified by covert video surveillance. *BMJ* 1987;294:1637–41.

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CURRENT PROBLEMS

Implications of the Children Act 1989 for paediatric practice

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The Children Act 1989 will, it has been said, when implemented bring about the most fundamental change of child law this century.[1] Yet there must be a risk that members of the medical profession and of the other professions concerned with the welfare of children will not at first appreciate the significance of the new legislation in terms of their own contribution. The objective of this article is to provide—at the cost of a considerable degree of oversimplification—an outline of the main changes made by the act that are likely to have an impact on paediatricians in court related work.

Act not concerned with criminal law

It is important to stress at the outset that the act is concerned with the *civil* law. (A care order may, however, still be made in certain circumstances where a child is proved guilty of a criminal offence, and the Children Act does make some minor amendments to the relevant provisions: see schedule 12 paras 20–30.) It is in particular concerned with resolving disputes between individuals (for example, parents who are divorcing) about the upbringing of children, and with the question whether the state is to be entitled to take compulsory measures—perhaps involving permanent removal from the parents—to secure the child's welfare. The act is not directly concerned with *criminal* proceedings. Criminal proceedings involve an allegation that the defendant has committed one or more of a number of narrowly defined criminal offences (for example, incest). The primary object of criminal proceedings is the punishment of the offender; the primary—perhaps the only—object of the civil law in this context, however, is to secure the welfare of the child. Hence, criminal proceedings, which remain largely unchanged by the Children Act, emphasise the need to protect the innocent against being convicted. Accordingly there are stringent rules about the admissibility of evidence and about the standard of proof that must be satisfied before an individual can be convicted. In contrast, the civil courts, concerned with the welfare of the child, are reluctant to allow legal technicalities to be allowed to interfere with the court's task in assessing where that welfare lies. It is because of this difference of emphasis that, for the lawyer, there is nothing remotely inconsistent in saying that there is insufficient evidence to justify prosecution of a suspected abuser, yet finding in civil proceedings that the child's welfare dictates an outcome that the parents strongly oppose.

Key concepts in the Children Act

The aim of this article is to give a general account of the structure of the act under the following headings. (1) Who is, in principle, legally entitled to take decisions affecting a child? (2) In what circumstances may individuals or public agencies bring issues relating to a child before the court? (3) If issues are properly brought before the court, what tests will the court apply in resolving those issues? (4) If the court decides that some intervention would be appropriate, what form can that intervention take—what orders can the court make? (5) What emergency powers do the courts have to protect children? (6) How will the act affect medical practitioners?

It is not intended to focus narrowly on the specific problems likely to arise in medical practice, but it is hoped that an outline of the new legal structure may assist in understanding the implications of the legislation for the medical profession. The concluding part of the article seeks to highlight some aspects of the impact that the act is likely to have in this respect.

(1) Decision taking and parental responsibility

In recent years the law has greatly restricted the rights of a parent to take decisions relating to the child's future. First, in 1969, the Family Law Reform Act (section 8) effectively made 16 the age of majority for medical treatment purposes. It specifically provided that if a 16 year old gave an effective consent it should not be necessary to obtain any consent from the parent. Secondly, in 1985 the House of Lords in the Gillick decision held that—as a general principle of the law—parental authority does not continue up to any specified age but gives way to the right of a child who has sufficient understanding and intelligence to decide matters for him or herself.[2] (The question whether a child *does* have the appropriate degree of understanding is an issue of fact in each case, and depends—among other things—on the complexity of the particular issue involved: hence, for example, a 14 year old might be capable of deciding on minor surgery under local anaesthetic, but not on purely cosmetic surgery involving a significant level of risk, and certainly not on non-therapeutic procedures.) Thirdly, the courts have asserted the paramountcy of the child's welfare—as distinct from the parent's rights—in deciding on those cases that do come before the courts. Thus the court could and did overturn a mother's decision taken in reliance on proper professional advice from a consultant paediatrician and from a consultant gynaecologist because it did not agree that the procedure in question would best serve the child's interests.[3] It may even be the law that certain procedures—for example, irreversible sterilisation—should not in any event be carried out on the authority of the parent unless prior court approval has been obtained.[4] (This view was expressed by only one member of the House of Lords, but the prudent will act on it.)

Notwithstanding this substantial erosion of parental decision taking power, it remains a basic legal principle that a child does not have legal capacity, and accordingly parents or others must be entitled to act on the child's behalf. The Children Act does not greatly change the structure of the law in this area, but the statutory definition ('parental responsibility') of the collection of rights, powers, duties, and responsibilities which an adult is entitled to exercise in this way is none the less a key concept. This is because it is the person who has parental responsibility who—subject to the restrictions referred to above—is entitled to act on the child's behalf.

The act provides that the following have 'parental responsibility':

(i) The *mother and father* of a legitimate child (or the *adoptive parents* of a child who has been legally adopted).

(ii) The *mother* of an illegitimate child. (The act does allow the mother and father to make a formal agreement in prescribed form whereby parental responsibility will be shared between them, but in the absence of such an agreement in the proper form or of a court order, the natural father of an illegitimate child does *not* have 'parental responsibility'.)

(iii) A guardian—the person appointed (by will or other document) to act as the child's guardian—usually only when there is no-one else who has parental responsibility.

(iv) Finally, certain persons—for example a person with whom the child is to live under what is called a residence order (see below) and a local authority in whose favour a care order has been made—have parental responsibility as an automatic consequence of a court order.

Broadly speaking, a person who has parental responsibility may act alone; and the act imposes no requirement of consultation with others having parental responsibility. Hence it will, for example, only be necessary to obtain the authorisation of *either* the mother or the father of a legitimate child.

There are, of course, circumstances in which a person who does not technically have parental responsibility may properly act to safeguard the child: in particular, the Children Act specifically provides that a person who had the care of a child may 'do what is reasonable in all the circumstances of the case for the purpose of safeguarding or promoting the child's welfare' (section 3(5)). (Generally speaking, references to specific provisions of the Children Act are only given in this article where the precise wording may be thought exceptionally significant.) Moreover, it seems that a person who has parental responsibility may authorise another person or persons to act on the parent's behalf (section 3 (9)). Surrender or transfer of parental responsibility as a whole, however, is forbidden.

The significance of the provision that any person who has 'parental responsibility' may act without the concurrence of others is greatly increased because of the legislative policy that parental responsibility is much more difficult to shift than was formerly the case. For example, in divorce the court will no longer make a 'custody' order—which, at one time, was thought to give the custodial parent virtually complete decision taking power—but instead may make a 'residence order', naming the person with whom the child is to live (and, as an automatic consequence, giving that person parental responsibility). But such an order will *not* deprive those who would otherwise have parental responsibility of their legal authority. If it is thought to be in the child's interest to prevent the non-resident parent from exercising legal authority the court will have to make a specific order to that effect. Even if a care order—which gives parental responsibility and the right to keep the child in care to a local authority—is made, the parents or others who had parental responsibility will still retain their legal authority. This could of course create a potentially explosive and impossible situation; and accordingly the local authority may decide to restrict the extent to which a parent or guardian may meet his parental responsibility if it is satisfied this is necessary in order to safeguard or promote the child's welfare (section 33 (3)(4)).

(2) Intervening in family autonomy: the right to bring matters to the court

How can issues affecting a child's future be brought before a court? This might appear to be an arid technical issue that can safely be left to the lawyers, but in fact the answer to the question determines the—often extremely sensitive—issue of whether a person (such as a child's grandparent or a local authority) can bring parental decisions for scrutiny by a court.

There are four main ways in which issues may be brought before the court.

(i) Wardship

Firstly, it will remain possible for any individual to make a child a ward of court by the simple procedure of issuing a summons; and the Children Act does not directly affect the right of *private individuals* to use this procedure. A child automatically becomes a ward on the issue of the summons, and thereafter (so long as the child remains a ward) no important step in the child's life may be taken without leave of the court. It was, for example, by the use of wardship that a concerned social worker was able to bring to the court the mother's decision to permit her handicapped daughter to be sterilised; and it was by wardship that a commissioning parent was able to have the future of a surrogate mother's child resolved by the court.

Although the Children Act does not affect the availability of wardship in such cases, it does make an exceedingly important change in relation to the use of wardship by local authorities. The rule will be that, in principle, local authorities will not be able to use wardship. They will accordingly not be able to interfere in family autonomy unless they can satisfy the new statutory threshold provisions—as set out below—for bringing care proceedings under the Children Act. In the past, some local authorities have made frequent use of wardship where difficult medical issues have been involved; but they are unlikely to be able to do so in the future, and medical practitioners will need to understand the considerable impact of this change in the law. In essence, whereas in wardship it was only necessary to satisfy the court that a certain course of action would serve the child's interests, the local authority will be dependent on proceedings in which the child's welfare does not become a consideration unless and until a statutory threshold condition—the 'significant harm' test—has been made out.

(ii) Divorce and other proceedings

The second main way in which proceedings affecting a child may come before the court is in numerical terms by far the commonest: it is in consequence of parental divorce proceedings. Whenever there is a divorce affecting children the court has to be given details of the arrangements that are to be made for their upbringing and welfare, and the court has a duty to consider whether to exercise any of the powers—powers now conferred by the Children Act—which it has in respect of those children. The act changes the filtering system whereby cases which ought to be investigated are identified. It also changes the language that will be used in orders, but it does not affect the principle governing the exercise of those powers: what would best serve the child's interests?

(iii) Freestanding private law applications

The act provides that certain people are entitled, as of right, to apply to a court for any of the orders relating to the child's upbringing dealt with below: this favoured group are the parents and other people with parental responsibility under the rules set out above. This group effectively is intended to define those whose interest in the child's upbringing is considered to be self evident.

A rather broader category of people are entitled to apply for orders dealing with specified matters: where the child should live, or what contact should there be between the applicant and the child? This class includes step parents, and anyone with whom the child has lived for a period of at least three years (subject to exceptions in the case of local authority foster parents). Effectively, therefore, this group is intended to cover people who are thought to have a legitimate right to claim an ongoing relationship with the child, but who should not necessarily have the right to seek the court's intervention on such specific issues as (for example) whether the child should receive medical treatment of a certain kind.

Finally, in pursuance of what is sometimes called the 'open door' policy the act permits *any* person to apply to the court for *any* of the orders referred to below, *provided* that the court has first granted leave. The act specifies matters to which the court is specifically to have regard in entertaining applications for leave—for example, what is the nature of proposed application? What risk is there that the proposed application would disrupt the child's life and cause him harm? What connection does the person concerned have with the child? A grandparent, therefore, might reasonably expect to be treated more favourably than a representative of a pressure group.

What it may well be asked is the association between all this and wardship? The act, as has already been mentioned, does not restrict the right of private individuals to start wardship proceedings, so why should anyone bother to seek leave to bring Children Act proceedings? No categorical answer to that question can be given; but it may be that the expense of wardship—only available in the High Court—will be a factor, particularly if restrictions are placed on the availability of legal aid.

(iv) Care proceedings, etc

Local authorities have extensive powers and duties to promote the welfare of children and in many ways it is the provisions of part III of the Children Act dealing with local authority support for children and families that are capable of having the greatest impact for good. The taking of compulsory measures by local authorities is often the last resort, and here the act takes a firm stand of principle: compulsory state intervention requires special justification. Indeed, the Lord Chancellor has said that although a broad welfare discretion may be appropriate and defensible where a court is deciding a dispute between warring members of a family, compulsory state intervention in the integrity and independence of the family can only be justified on the basis of defined minimum criteria. To do otherwise (it is said) would constitute a threat to the poor and minority groups, whose view of what is good for a child may not coincide closely with that of the majority.

The result of this approach is that the court may only make a care order (or a supervision order—that is, an order putting the child under the supervision of a local authority) if the so called 'significant harm' criterion is satisfied.

What is meant by the 'significant harm' test? The act provides that the court may only make a care or supervision order if it has first of all found: (a) that the child concerned is suffering, or is likely to suffer, significant harm; and (b) that the harm, or likelihood of harm is attributable to either the care given to the child, or likely to be given to him if the order were not made, not being what it would be reasonable to expect a parent to give to him, or the child's being beyond parental control.

The statutory provision bristles with difficulty; and it is reasonable to suppose that there will be a great deal of litigation in the early days until principles are settled. (The act further defines 'harm' as 'ill treatment or the impairment of health or development'; 'development' means 'physical, intellectual, emotional, social, or behavioural development'; 'health' means 'physical or mental health'; and 'ill treatment' includes sexual abuse and forms of ill treatment which are not physical: section 31(9).) But—whatever the precise meaning of the statutory text—it is vital to emphasise that, although the court must be satisfied by evidence that the specified criteria have been established before it can make a care order or a supervision order, proof of the statutory criteria is simply a *necessary* condition for court intervention. Such proof is not a *sufficient* condition. The court will—as we shall see—also have to be satisfied by evidence that the making of an order would be better for the child than making of no order at all. It will have to regard the child's welfare as its paramount consideration, and it must have regard 'in particular' to certain specified matters relevant to welfare.

(3) Principles applied by the court in resolving issues

The child's welfare is the court's paramount consideration in determining any question with respect to a child's upbringing. The act provides a 'checklist' of factors that may be relevant. It also lays down other relevant principles (including the so called 'non-intervention' principle and a presumption about the effect of delay). It also contains a number of pointers about the desirability of promoting contact between a child and the family.

(i) The welfare checklist

The Children Act enumerates a number of matters relevant to welfare that are intended to guide the courts, achieve consistency, and encourage the parties to disputes to concentrate on issues relevant to the children's welfare. These are:

'(a) the ascertainable wishes and feelings of the child concerned (considered in the light of his age and understanding);

(b) his physical, emotional and educational needs;

(c) the likely effect on him of any change in his circumstances;

(d) his age, sex, background, and any characteristics of his which the court considers relevant;

(e) any harm which he has suffered or is at risk of suffering;

(f) how capable each of his parents, and any other person in relation to whom the court considers the question to be relevant, is of meeting his needs;

(g) the range of powers available to the court under this Act in the proceedings in question'.

These matters may be considered in any case, and will no doubt be found helpful in many. But the court *must* consider them—in effect it will have to go through the list in turn—in cases where a local authority seeks a care or supervision order and in cases where there is a *disputed* application in divorce or other family proceedings.

(ii) The presumption that delay is harmful

The Children Act specifically provides that the court should have regard to the 'general principle' that any delay is likely to prejudice the welfare of the child (section 1(2)). This is not, of course, to say that in some cases delay—for example, pending the exploration of alternative measures which might be taken—could not be beneficial. But the onus is on those who want to displace the general principle to do so by evidence.

(iii) The non-intervention principle

The Children Act provides that where a court is considering whether or not to make one or more orders under the act with respect to a child, it shall not make the order or any of the orders unless it considers that doing so would be better for the child than making no order at all (section 1(5)).

This non-intervention principle is arguably the most important single provision in the act. First, it clearly embodies the philosophy that the court does not necessarily know better than the parents what is for a child's benefit and that accordingly it should not interfere unless the court is satisfied that its interference will do good. Secondly, the act also accepts that the law is a blunt instrument. The making of orders—enforceable, in the last analysis, by the sanction of imprisonment—is not always the most effective way of achieving the best outcome, or the least detrimental outcome, that could be achieved for the child.

It seems reasonable to suppose that the non-intervention principle will be invoked in many cases—particularly, perhaps, by advocates in care cases. It will be argued that, even if the significant harm threshold is satisfied, there is no evidence that the making of the order could be better for the child than, for example, making an order that the child live with grandparents or a friend, or even leaving things to voluntary collaboration between the family—adequately supported by social services and other relevant agencies—and the local authority. Again, the need for expert evidence about the likely impact of the various options requires no emphasis.

(iv) Promoting contact

The Children Act embodies an assumption that continued contact between a child, parents, and the family is in principle desirable. For example, before making a care order, the court is to consider arrangements proposed for contact. If a care order is made the authority is obliged, subject to any court order to the contrary, to allow reasonable contact, and the court has powers to entertain applications for contact with the child. Again, the question of whether contact is desirable in the particular circumstances of the case is a matter on which expert evidence seems certain frequently to be required.

(4) Orders the court can make

Under the old law, still in force at the time of writing, different courts had different powers, and proceedings affecting the same child might be pending at the same time in different courts. The Children Act will introduce two major simplications. First the court will (for present purposes) have the same powers whether it be the High Court, the county court, or the magistrates court (which is to be renamed the 'family proceedings court'). There is to be provision to try to ensure that cases are dealt with at the appropriate level of judicial expertise—so that one would expect a complex case involving the assessment of detailed psychiatric or other medical evidence in a contested abuse case to be dealt with by the High Court. The family proceedings court would deal with the majority of the less complex cases in which local authorities seek care orders.

The second change is that all the courts concerned will be able to make the same orders selected from what is described as a 'menu'. These orders are defined in the act as follows:

Contact order: an order requiring the person with whom a child lives, or is to live, to allow the child to visit or stay with the person named in the order, or for that person and the child otherwise to have contact with each other.

Prohibited steps order: an order that no step which could be taken by a parent in meeting his parental responsibility for a child, and which is of a kind specified in the order, shall be taken by any person without consent of the court.

Residence order: an order settling the arrangements to be made as to the person with whom a child is to live.

Specific issue order: an order giving directions for the purpose of determining a specific question which has arisen, or which may arise, in connection with any aspect of parental responsibility for a child.

Family assistance order: an order requiring a probation officer or officer of a local authority to be made available to advise, assist and (where appropriate) befriend the child, or any parent or guardian, or any person with whom the child is living or in whose favour there is a contact order in force.

The above orders can be made, as stated above, whenever the child's welfare requires it in any 'family proceedings'. The act defines that term; but for present purposes it is sufficient to note that the court could for example make a residence order (in favour of a grandparent, perhaps) in a case where the applicant had asked for an adoption order. Again, as already mentioned, the court could make a residence order in care proceedings. It could even order that the child remain with the mother in the family home on condition that the father left and only had contact with the child perhaps under supervision or in certain specified circumstances. (The act in fact gives local authorities special powers to facilitate such a solution, which might be useful in some abuse cases.)

Care and supervision orders may also be made in any 'family proceedings'; but as has already been emphasised, only if the court has satisfied itself that the 'significant harm' test has been met. Moreover, the local authority will have to go through the formality of applying for the order. There may, of course, be cases in which the court hearing a divorce case (for example) considers that a care order would be the most satisfactory remedy. In that case it may require the local authority to investigate and to consider whether to make an application for such an order.

(5) Emergency provisions

The act contains two main emergency remedies for protecting the child who is thought to be exposed to the *risk* of significant harm. First, the court may make an *emergency protection order* if there is reasonable cause to believe that the child is likely to suffer significant harm or if inquiries are being frustrated by the denial of access. To some extent such an order is the counterpart of the existing place of safety order, but an emergency protection order can only last for a comparatively short period (eight days) and is extendable once for a further seven more days. It is important to emphasise that both the welfare test and the no order presumption principle apply to an application for an emergency protection order.

In terms of the medical profession's involvement, it should be noted that the act specifically provides that the court making an emergency protection order may give directions for medical or psychiatric examination or other assessment of the child. It is also provided that a child of sufficient understanding may none the less refuse to submit to the examination or other assessment. It is to be expected that guidance will be given about the profession's responsibilities under this provision.

The second protective measure is the *child assessment order*. Such an order may be granted where the applicant has reasonable cause to suspect that the child is suffering or likely to suffer significant harm, that assessment of the child's health, development, or treatment is necessary to decide this, and that it is unlikely that such an assessment will be possible unless the court makes an order to that effect. The order requires any person who is in a position to produce the child to do so, and to comply with such directions relating to the assessment of the child as the court thinks fit to specify in the order. The order will specify what is to be done under the order—normally to carry out an assessment of the child's health or development—and it authorises any person carrying out the assessment 'to do so in accordance with the terms of the order'. Again, the Children Act provides that a child of sufficient understanding to make an informed decision may refuse to submit to a medical or psychiatric examination or other assessment.

Child assessment orders are not intended to be soft options: if the court considers that there is ground to make an emergency protection order it should do so; and a child may only be kept away from home under a child assessment order in accordance with the terms of that order and so far as is necessary for the purposes of the assessment and for such period or periods as may be specified in the order.

(6) Impact of the act for medical practitioners

This article has been primarily concerned to sketch the broad structure of the act, rather than to attempt to analyse the specific responsibilities that are likely to be placed on the medical profession as a result of its implementation. But it may be helpful to indicate certain general consequences for medical practice that seem likely to follow:

(i) In routine general and hospital medical practice, it will be necessary for there to be a broad understanding of the principles of parental responsibility, particularly in terms of the power to give a valid consent to medical procedures. Again, the right of a child of sufficient understanding to refuse to undergo medical examination is of self evident importance to the profession.

(ii) It is likely that medical assessments (including, of course, psychiatric assessments) will be called for on a much greater scale than has been the case in the past. In particular, it would seem difficult for courts to decide the issue of 'significant harm' without hearing an evaluation of the effect of what has happened to the child. Again it is not easy to see how a court could properly decide whether the making of an order would be better for the child than not doing so without being able to weigh up the developmental and other factors involved.

In essence, therefore, it would seem that courts are likely to require much more by way of expert assessment, and a significant proportion of this will be medical assessment. In private law cases doctors are likely to be involved either on the instructions of solicitors acting for one of the parties involved, or in collaboration with a *welfare officer* acting under an order made by the court in any proceedings. In care proceedings a *guardian ad litem* is to be appointed to represent the interests of the child unless the court is satisfied that it is not necessary to do so in order to safeguard the child's interests. In many cases the guardian will require medical assistance to decide on the recommendations which should be made to the court.

1 Lord Mackay of Clashfern. *House of Commons Official Report (Hansard)* 1988; vol 502 col 488.
2 Gillick v West Norfolk and Wisbech Area Health Authority [1986] AC 112.
3 Re D (A minor) (Wardship: sterilisation) [1976] Fam 185.
4 Re B (A minor) (Wardship: sterilisation) [1988] AC 199.

See related article on p457.

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Maternal and child health problems in the USSR

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This is the first paper in a series showing the problems facing the medical services for children in different countries.

The mother and child health services of USSR are currently facing a number of acute unsolved problems. The priority tasks stipulated in the resolution of the Central Committee of the USSR Communist Party and of the Council of Ministers of the USSR dated 19 November 1987 and entitled 'The principal lines of development of public health and of the reconstruction of USSR health services in the twelfth five year plan and in the period to year 2000' are being realised very slowly and a number of considerable difficulties are being encountered.

In the first place, priority funds for obstetric and paediatric services so far have not been secured. The experience in various areas of the country in the new economic climate shows that the USSR Ministry recommendations are being ignored locally and that correction coefficients have to be introduced when the finances per head of population with due consideration of the age/sex distribution are being calculated.

Secondly, the realisation of the All-Union Congress of Doctors resolution on abolition of the 'departmental medicine' and creation of a unified health service on the geographical principle is being delayed. Two parallel (departmental and geographical) structures of adult health services often duplicate each other and, when funded from a single source, are an intolerable burden on local budgets. Obstetric and paediatric services can thus be funded only by residue financing and consequently become subject to severe economies.

Thirdly, so far attempts to secure additional central funds for pressing specific needs in the field of mother and child services, such as family planning, genetic counselling, early (childhood) prevention of invalidity, vitamin administration to pregnant women and children, etc, have proved unsuccessful.

These general shortcomings in the provision of mother and child services are compounded by certain persistent personal attitudes. Still far from all party managers at various levels and health service administrators have recognised the futility of endeavours aimed at improving the health of the population without radical changes in the investment policies in favour of mother and child care.

For these reasons the materiel-technological basis of obstetric and paediatric services remains unsatisfactory. For instance, in 1989, the number of new obstetric/paediatric beds accounted for only 17% of all new beds brought into use and that of paediatric and obstetric/gynaecological units for only 11% of all new outpatient/polyclinic establishments. The increases in the number of paediatric, obstetric, and labour beds have lagged behind the growth of these groups of population. Consequently, in various republics (Turmenskaya, Uzbekskaya, Tadzhikskaya, Kirgizskaya, and Azerbaidzhanskaya SSRs) the numbers of paediatric/obstetric/labour beds represent drops by factors of 1·5–2 below the requirements. Even the beds lost are not being currently replaced.

Close to 50 administrative territories have no autonomous district paediatric hospitals; 25 000 paediatric beds are situated in condemned buildings. The floor area per mother/child bed has been reduced by the factor of 2·5. Overcrowding in maternity hospitals continues to cause outbreaks of infections.

The total number of paediatric beds for treatment of infectious diseases in the country is 2·5 times below the requirement and 70% of paediatric infectious disease hospitals are grossly overcrowded and occupy non-purpose built but adapted buildings, often without drainage/sewerage and without either cold or hot water supply.

Further reductions of maternal and neonatal mortality in the country largely depend on securing the appropriate technical equipment levels in the paediatric treatment/prevention units and obstetric establishments. At present the shortcomings in this area are very great indeed and in some respects only 30–40% of requirements are satisfied.

An analysis of equipment levels in various geographical areas showed that the paediatric/obstetric services are clearly lagging behind the adult network. For instance, the mean figure for medical technological funding for republic and oblast (district) hospitals for adults equals 2·75 thousand roubles per bed, as against 1·02 thousand roubles per paediatric bed; the corresponding figures for city hospitals are 1·27 and 0·7 thousand roubles. In Kirgizskaya SSR the figure for obstetric hospitals was 0·5–0·18 thousand roubles, for the republic paediatric hospital—0·7 thousand roubles, for oblast paediatric hospitals—0·2 thousand roubles and for regional hospitals—0·050–0·059 thousand roubles. In the Russian Soviet Federative Socialist Republic (RFSSR) the medical technological funding per adult bed was 2·5 times below that per paediatric bed. The same situation was found in the Ukrainian SSR.

Gross shortages are also being experienced in the provision of drugs. Requests for supplies of such important groups of medicaments as enzymes, biopreparations, immunoglobulins, haematinics, and blood substitutes are met in only 30–60%.

However, discussion of the difficulties and unresolved problems alone could not be justified. A board meeting in the Ministry of Health of the USSR held on 31 January 1990 discussed the present state of affairs, as well as the measures required to satisfy the technological requirements, the funding and the materiel supplies of the paediatric and obstetric treatment and prevention units. A number of vital resolutions were adopted. These were designed to secure the necessary finances for the principal lines of the mother/child services, to eliminate the funding deficiencies in mother/child treatment and prevention units and earmarked no less than 40% of the available capital for construction of mother/child establishments and development of medical technology. A decision was also made to extend the scope of the existing and newly constructed diagnostic units to investigation of women and children. For this purpose the units will receive the necessary additional apparatus and equipment.

Resolution No 1120, dated 21 December 1989, of the Council of Ministers of the USSR stipulated separate financing, as from 1 January 1990, of labour beds and neonatal beds and thus provided means for resolving many supply problems in maternity hospitals. The same resolution increased the food funding to 2 roubles in paediatric hospitals and sanatoria. The list of diseases qualifying for free issue of drugs in outpatient clinics has been increased to include infantile cerebral palsy, SPID with early genital development, as well as all pregnant women and children domiciled in the areas affected by the Chernobyl disaster.

Table 1 Infant mortality rates in the USSR and in the individual soviet republics

Administrative area	*First year death rates/1000 live births*		
	1988	*1989**	*Variation in absolute number (%)*
USSR	24·7	22·3	−2·4 (− 9·7)
RSFSR	18·9	17·3	−1·6 (− 8·5)
Ukrainskaya SSR	14·2	12·6	−1·6 (−11·3)
Belorusskaya SSR	13·1	11·5	−1·6 (−12·2)
Uzbekskaya SSR	43·3	37·5	−5·8 (−13·4)
Kazakhskaya SSR	29·3	25·4	−3·8 (−13·0)
Gruzinskaya (Georgian) SSR	21·9	19·4	−2·5 (−11·4)
Azerbaidzanskaya SSR	27·0	26·0	−1·0 (− 3·7)
Litovskaya (Lithuanian) SSR	11·5	10·7	−0·8 (− 7·0)
Moldavskaya (Moldavian) SSR	23·0	19·6	−3·4 (−14·8)
Latviiskaya (Latvian) SSR	11·0	10·9	−0·1 (− 0·9)
Kirgizskaya SSR	36·8	32·5	−4·3 (−11·7)
Tadzhikskaya SSR	48·9	43·2	−5·7 (−11·7)
Armyanskaya (Armenian) SSR	25·3	20·5	−4·8 (−19·0)
Turkmenskaya SSR	53·3	54·2	+0·9 (+ 1·7)
Estonskaya (Estonian) SSR	12·4	14·6	+2·2 (+17·7)

*Only interim data are available for 1989.

Revision of service priorities led to important advances in the development of the materiel-technological basis; 75 laboratories for prenatal diagnosis of fetal infections and 30 laboratories for neonatal hypothyroidism screening were purchased in 1988–9. In the last year purchases of resuscitation equipment and of incubators for premature babies increased by the factor of two; rehydration equipment requirements have been fully satisfied.

Compared with 1988, the neonatal mortality dropped by 9·7% (table 1). The greatest drops were recorded in the Belorusskaya, Uzbekskaya, Kazakhskaya, Moldavskaya, and Armianskaya SSRs. However, in Estonskaya and Turkmenskaya SSRs infant mortality increased and this finding calls for a thorough investigation.

The relative importance of causes of infant mortality continue to vary (table 2). In 1989 the list was headed by perinatal factors and, for the first time, the incidence of endogenous (congenital and perinatal) exceeded that of exogenous causes (infections and respiratory tract diseases), at 45·9% and 45·1% respectively.

Without exaggerating the importance of favourable statistical shifts, the latter appear clearly linked to the realisation of regional programmes designed to reduce mother and child mortality figures. These programmes deserve thus close attention and must be pursued with maximum energy (table 3).

One of the main efficacy indices of mother and child health services is the maternal mortality rise. In USSR this figure is high; in 1988 it was 43 per 100 000 newborn, that is, four times

Table 2 Relative incidence of causes of infant mortality in USSR. Results are number/1000 (%)

Cause	*1981*	*1985*	*1988*	*1989**
Infections and parasitic diseases	4·5 (16·8)	4·1 (15·8)	3·8 (15·4)	3·3 (14·8)
Respiratory tract diseases	11·0 (41·0)	10·1 (38·9)	7·8 (31·6)	6·8 (30·5)
Congenital defects	3·0 (11·2)	3·3 (12·7)	3·2 (13·0)	3·1 (13·9)
Perinatal conditions	5·5 (20·6)	6·0 (23·1)	7·0 (28·3)	7·2 (32·3)
Other	2·8 (10·4)	2·5 (9·6)	2·9 (11·7)	1·9 (8·5)
Total	26·8 (100·0)	26·0 (100·0)	24·7 (100·0)	22·3 (100·0)

*Only interim data are available for 1989.

Table 3 Principal directions of medical activity in the regions with different maternal and infant mortalities

Levels of maternal and infant mortality		
Low	*Intermediate*	*High*
(1) Early diagnosis and prognosis of unfavourable outcome of pregnancy and of hereditary and congenital diseases	(1) Family planning—fight against induced abortions	(1) Family planning—increased spacing of births
(2) Family planning—fight against induced abortion	(2) Early diagnosis and prognosis of unfavourable outcome of pregnancy and of hereditary and congenital diseases	(2) Development of hospital and extrahospital first aid, resuscitation and intensive care services
(3) Medicosocial assistance for at risk social groups	(3) Development of hospital and extrahospital first aid, resuscitation and intensive care services	(3) Rational diet for pregnant and breast feeding women
(4) Attention to health hazards and general improvement of working conditions of women	(4) Attention to health hazards and general improvement of working conditions of women	(4) Attention to health hazards and general improvement of working conditions of women. Instruction in healthy life

the figure reported in the Federal Republic of Germany, six times that in the UK and USA figures, and 15–20 times the Canadian and Scandinavian ones.

Because of irregularities in medical death certificates and resulting underregistration by USSR State Statistical Office, however, these maternal mortality figures are unreliable. For instance, in 1988, ZAGS offices* underregistered 479 deaths and the actual maternal maternity rate was 51·9 per 100 000 live births, which was 17% more than the USSR State Statistical Office figure. When all deaths pertaining to maternal mortality figures are taken into account, the true index for many individual republics exceeds the USSR State Statistical Office figure by a factor of 2 or more, and more exactly by a factor of 2·6 for Turkmenskaya SSR, 2·2 for Gruzinskaya SSR, 1·7 for Uzbekskaya SSR, and 1·6 for Tadzhikskaya SSR.

To provide means for systematic follow up of maternal mortality rates the Minister of Health of the USSR introduced special regulations for reporting of all cases of maternal deaths, with effect from 1 January 1990.

Another important efficacy index of mother and child health services is the perinatal mortality rate and this has remained high for a number of years: in 1988 it was 17·3 per 1000 live and stillbirths. The figures for individual republics ranged from 8·7 per 1000 for the Litovskaya SSR to 25·2 per 1000 for the Tadzhikskaya SSR. The profile of causes of perinatal mortality in the last three years remained unchanged and has been headed by asphyxia (50·8%, of all perinatal deaths), followed by respiratory diseases (17·6%), congenital anomalies (12·9%), and birth injuries (7·2%) in that order. Examination of maternal causes of perinatal mortality shows that the diagnosis 'cause not established' accounts for 24·6% of all fetal and newborn deaths, while extragenital maternal pathology accounts for 16·1%, placenta praevia and placental separation for 11·9% and late toxaemia for 11·1% of the overall figure.

A rather frightening finding is the high proportion of full term neonates in perinatal losses. In 1988 it amounted to 51·8% of all stillbirths and deaths in the first six neonatal days. In various national statistics full term perinatal deaths do not account for more than 25% of perinatal mortality. This finding indicates poor antenatal and delivery supervision, as well as unsatisfactory organisation of neonatal care. The fact that an increasing fraction of stillbirths is attributed to antenatal death (in utero) (from 44% in 1980 to 56% in 1988) further confirms these inadequacies; the 1988 index for the Tadzhikskaya SSR was 70%.

The stillbirths/early neonatal mortality ratio for the USSR was 1·3:1. This value approached 1:1 for the Baltic republics and 2:1 for the Tadzhikskaya, Turkmenskaya, and Azerbaidzhanskaya SSRs.

From the statistical point of view the fact that stillbirth mortality rates exceed early neonatal mortality rates by a factor of close to two suggests that early (in the first few hours) neonatal deaths are grouped with stillbirths and also that organisational aspects of intensive care and resuscitation of the newborn require close reexamination.

Another pressing problem facing the medical services of the country as a whole is the need for reduction in the number of induced abortions and prevention of unplanned pregnancies. Induced abortion is recognised as a frequent cause of infertility, miscarriage, other complications of pregnancy and labour, and of high maternal and infant mortality rates. The losses to economy caused by induced abortions and the resulting gynaecological morbidity amount to over 1000 million roubles yearly. The number of induced abortions in USSR in 1988 was over 7 000 000, meaning that in that year 3500 obstetrician-gynaecologists were fully occupied on these procedures alone. The number of induced abortions per 1000 women of childbearing age in USSR is among the highest in the world: 103·7 (1988), as against 10·2 in Canada, 12·4 in Finland, 12·8 in the UK, and 14·9 in France. The number of induced abortions in primigravidae under 17 years of age is increasing and every fifth induced abortion in this age group is done outside hospital services. The incidence of induced abortion related complications is not falling and fatal outcomes are not unusual. In the last three years the number of induced abortion related deaths was 2020 and 76·7% of these deaths were due to complications of abortions performed outside hospitals. Despite the measures adopted the preventive work in this area can not be accepted as adequate. Local family planning services are grossly underdeveloped. In USSR only 13·5% of women of childbearing age use modern effective means of contraception, while the corresponding figures for developed countries range from 60 to 80%.

The main cause of this highly unsatisfactory state of affairs in the field of family planning and of fight against induced abortions is the lack of modern contraceptives. The seriousness of the problem has been compounded by the mistaken belief shared over many years by Soviet scientists and the workers of the USSR Ministry of Health that the use of hormonal contraceptives is not advisable because of the possible harmful side effects. These fears have been convincingly dispelled by the experience gained in Japan, USA, France, the Federal Republic of Germany, and other developed countries.

The USSR Ministry of Health is now examining the problem of family planning as a special branch in the context of mother/child health services. Scientific studies have shown that prevention of pregnancy in women under 19 and over 35–40 years of age, combined with spacing of births to not less than 2·5 years may reduce maternal mortality and early neonatal mortality rates by factors of 2 and 4 respectively. According to WHO figures the mortality rates for children whose births are spaced at less than one year are twice those for children born at intervals of two years or more.

These figures provide convincing guidelines for concentration of means and efforts required for the speediest possible reduction of maternal and infant mortality rates. Family planning facilities must be provided in all treatment and prevention centres, starting with feldsher (nurse-practitioner)-midwife units, and educational work must be widely intensified and should involve television, press, and religious workers.

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*Local (or zonal) death registration bureau.

At present the problem of creation of a Soviet contraceptive industry is being discussed at the state level. The amounts of modern contraceptives imported from abroad increased in 1990 by a factor of 2·5.

One of the pressing problems of primary medical care is radical re-examination of our approach to mother/child care in rural areas, where the discrepancies in the levels of health services are particularly evident. Of the whole population of USSR, 40% of women and 43% of children live in rural areas, and in the central Asian republics the figures are over 60%. Unlike the towns and cities, in the last five years the rural areas saw no reduction in infant mortality rates which remained 32·6% higher, compared with the urban figures. Rural maternal death rates are also high; they account for 54–57% of all maternal deaths, and in central Asian republics and in Kazakhskaya SSR this figure reaches 60–80%. In depth examination of relevant data shows that, generally speaking, the state of health of women and children is considerably worse in the countryside compared with the towns and cities. One of the underlying reasons is poor medical care, particularly at the specialist level. In various parts of the USSR (Uzbekskaya and Gruzinskaya SSRs, Krasnoyarskii Krai, Kurskaya Oblast of RSFSR and others) the main hospitals (of the republic, region, or oblast) have no obstetric units and thus the inhabitants of rural districts, with serious obstetric and extragenital pathology, or with complex gynaecological problems are deprived of specialist care.

Nowadays, in the context of economic changes in the countryside involving new approach to health service funding with devolution of administration to lower levels, the first objective must be elimination of discrepancies in staffing. New nurse, midwife, and doctor posts must be established in central regional hospitals to allow formation of mobile mother and child care teams, the creation of day hospitals and domiciliary teams, and the provision of other forms of medical care delivery depending on local requirements.

Mother and child health service in USSR continues to present thus a number of problems. Their solution depends first of all on the quality of our individual and society efforts. Mindful of the need for prompt correction of the situation, the Minister of Health of the USSR prepared and passed on for consideration, by the USSR Council of Ministers and by the Supreme Soviet of USSR, a number of concrete proposals for urgent measures concerning health provisions for mothers and children.

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CURRENT TOPIC

Paediatric bone marrow transplantation using donors other than HLA genotypically identical siblings

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Allogeneic bone marrow transplantation using HLA genotypically identical sibling donors (ID-BMT) is generally accepted as curative treatment for a range of life threatening disorders of childhood affecting the pluripotent haemopoietic stem cell or its progeny. Disorders universally considered suitable for treatment by ID-BMT are those in which the probability of long term survival with a good quality of life is remote if alternative treatment is given. Uncontroversial indications for ID-BMT in childhood include severe aplastic anaemia,[1] severe combined immune deficiency,[2] and chronic myeloid leukaemia.[3] In strong contrast, there is little agreement among paediatric haematologists about whether ID-BMT should be used as definitive treatment for children with acute leukaemia with no particular risk factors.[4] Between these two extremes lie several disorders, including thalassaemia major,[5] in which an increasing number of paediatric haematologists are becoming more enthusiastic about including ID-BMT in their treatment protocols. Some principle indications for transplantation from an HLA identical sibling in childhood are shown in the table.

An important reason for the rising popularity of ID-BMT is the development of myeloablative regimens that exclude the use of total body irradiation. The most successful chemotherapy protocol is high dose busulphan combined with high dose cyclophosphamide.[6] Preliminary data from the Pesaro group on the long term follow up of patients who underwent bone marrow transplantation for β thalassaemia major suggest that busulphan and cyclophosphamide do not result in the failure of growth and development seen in young children who underwent transplantation and total body irradiation.[7] Despite these encouraging data it is almost certain that the vast majority of children who receive transplants and are treated with busulphan and cyclophosphamide will be as infertile as the recipients of total body irradiation.

Some major indications for bone marrow transplantation from an HLA identical sibling in childhood

Disorder	*Optimal timing for bone marrow transplant*
No controversy	
Severe aplastic anaemia	Before multiple transfusions
Fanconi's anaemia	Before multiple transfusions
Congenital immunodeficiencies	Before major infection
Chronic myeloid leukaemia	First chronic phase
Some controversy	
Poor risk acute leukaemias	First or second remission
Thalassaemia major	Before secondary organ damage
Congenital cytopenias	Before multiple transfusions
Inborn errors of metabolism	Before secondary organ damage
Major controversy	
Standard risk acute leukaemia	Second remission
Sickle cell anaemia	Before secondary organ damage

For most disorders it is generally agreed that ID-BMT should be carried out early before major complications occur and before malignant disorders become resistant to chemotherapy or irradiation.[8] Exceptions to this rule in childhood are acute lymphoblastic and acute myeloblastic leukaemias with no particular risk factors in which there is a good chance that the child will be cured by chemotherapy alone.[4] ID-BMT is usually reserved for patients in their second remission. Single centre studies and analysis of large data bases held by the European Bone Marrow Transplant Group and the International Bone Marrow Transplant Registry indicate that roughly 70% of patients with bone marrow failure with no particular risk factors and half of those with leukaemia become long term disease free survivors with a good quality of life after ID-BMT.[1,3]

The purpose of this review is to discuss the place of bone marrow transplantation in the treatment of children with haematological malignancies and bone marrow failure who lack a HLA identical sibling. Little data have been published on alternative donor bone marrow transplantation in childhood, and it is therefore difficult to make general recommendations. Some principles of donor and patient selection will be discussed, however, which may be helpful to those paediatricians who are considering alternative donor transplantation for children under their care. Formal clinical guidelines can only be established from the results of large prospective studies, such as the International Marrow Unrelated Search and Transplant (IMUST) Study which is currently in progress.[9]

Partially HLA matched family donor bone marrow transplantation

LEUKAEMIA

At present the size of families in Western Europe and North America dictates that only 30–35% of patients have a HLA identical sibling. The Seattle group has pioneered the use of partially matched family donor transplants as treatment for leukaemia. Results of their studies strongly suggest that HLA mismatch is only acceptable at the one antigen level.[10] In this study they showed that patients who received transplants from donors mismatched for two or more HLA antigens had an unacceptably high probability of graft failure,[11] or severe graft versus host disease.[10] As a result of this report family members who are phenotypically matched for HLA or are only mismatched by one HLA-A,B, or DR antigen with the patient are often considered suitable donors for patients with haematological cancers. If a phenotypically HLA matched, or one antigen mismatched, family member is available then the clinical indications for bone marrow transplantation are the same as for ID-BMT.

SEVERE APLASTIC ANAEMIA

It is less certain whether a family donor mismatched for one antigen should be used to give a transplant to a patient with severe aplastic anaemia. Most of the results published so far for partially matched donor bone marrow transplantation for this disease have been disappointing, with graft failure a frequent cause of death probably because of the large proportion of highly sensitised patients who receive transplants.[12 13] There was also an initial lack of appreciation that more intensive immunosuppressive protocols are required to achieve stable engraftment after partially matched family donor bone marrow transplantation than are needed in ID-BMT for severe aplastic anaemia. In a recent preliminary study Camitta *et al* used an intensive immunosuppressive protocol including total body irradiation and anti-T cell monoclonal antibody purging of donor marrow for prevention of graft versus host disease.[14] Results have so far been encouraging with more than half a small number of patients becoming long term survivors.

CONGENITAL IMMUNE DEFICIENCIES AND OSTEOPETROSIS

This is one area in paediatric bone marrow transplantation where the use of one haplotype (3 antigen) mismatched donors has been successful. In a European collaborative study Fischer *et al* reported long term actuarial disease free survival of 57% of patients with congenital immunodeficiencies using HLA haplomismatched family donors, mostly parents.[2] The success of these transplants was dependent on the use of intensive pretransplant immuosuppressive treatment to prevent graft failure, and T cell purging of the donor marrow to prevent graft versus host disease.

Limitations of mismatched family donor bone marrow transplantation

The main limitation of using HLA mismatched family members as alternative marrow donors is that (apart from in the congenital immunodeficiencies) the procedure is limited to donor recipient pairs with one HLA-A,B, or DR antigen mismatch by graft failure and graft versus host disease. This means that acceptable partially HLA matched donors only extend the famliy donor pool provided by HLA identical siblings by about 10%, leaving about 60% of potential recipients without a donor.

In certain circumstances an extended family donor search is worthwhile, although it is wise to consult an immunogeneticist before proceeding. Patients whose parents are first cousins may have a HLA phenotypically matched donor in their extended family. In other families in which both maternal and paternal relatives share one common HLA haplotype with the patient, there is a chance of finding a phenotypically matched relative. Extended family donor searches are most important for non-white patients because as will be seen later they have little chance of an HLA 'matched' unrelated donor.

HLA 'matched' unrelated volunteer donors

In the early 1970s the Anthony Nolan panel of HLA typed volunteer donors was set up as a collaborative effort between Mrs Shirley Nolan and Dr David James in the department of immunology, Westminster Hospital, London. Initially the panel's aim was to find a marrow donor for Mrs Nolan's son, Anthony, who had Wiskott Aldridge syndrome. After Anthony's death the panel was used to search for donors for patients with a wide range of diseases requiring treatment by bone marrow transplantation.[15] During the last five years several additional panels of unrelated donors have been set up in different European countries and in the United States and Canada. In the United Kingdom a second panel has been established at the United Kingdom Transplant Service in Bristol, and is made up of National Blood Transfusion Service donors. World wide roughly 300 000 HLA typed volunteers are available.

The selection of unrelated donors is at present complicated, time consuming, and expensive. Problem areas can be defined as follows:

(i) Which patients should be selected for unrelated donor searches?
(ii) How can unrelated donors be found for patients from ethnic minorities who often have different HLA phenotypes from the volunteer donors who are predominantly white?
(iii) Which HLA typing and matching tests are best for selecting unrelated donors?
(iv) How can the logistic problems of locating potential donors and obtaining and transporting blood samples for HLA matching be solved?

Patient selection for unrelated donor searches

EARLY REFERRAL

A recent analysis of unrelated donor searches done through the two registries in the United Kingdom, and entered into the IMUST study, showed a significantly increased risk of failure because of deterioration or death of the patient when searches were carried out for patients with advanced disease.[16] This is understandable as at present the median time taken for a donor search in the United Kingdom is six months.[17] At present therefore it is essential to consider the possibility of unrelated donor bone marrow transplantation (UD-BMT) as soon as possible after diagnosis, and to request a search if indicated.

CHRONIC MYELOID LEUKAEMIA

A recent retrospectively analysed study of UD-BMT in the United Kingdom showed that a predominantly adult group of patients with chronic myeloid leukaemia in the chronic phase survived longer after UD-BMT than patients with other disorders.[18] This finding is probably partly because the relatively long chronic phase characteristic of this disorder allows time for an unrelated donor search to be completed before the patient's condition deteriorates. At the Hammersmith Hospital the first 34 adult UD-BMT transplants carried out for chronic myeloid leukaemia gave similar results to ID-BMT for chronic myeloid leukaemia carried out over the same period of time. Chronic myeloid leukaemia is an unusual leukaemia in the paediatric age group, but when a child does present with it and without a suitable family donor, UD-BMT should be considered.

ACUTE LEUKAEMIA

Children with acute leukaemia and poor risk features at diagnosis are suitable candidates for early unrelated donor searches. As yet there is no consensus about whether UD-BMT should be carried out during the first or second remission. In one study 39 children received transplants for acute or choronic leukaemia from donors other than HLA identical siblings. Where an unrelated donor was available the patient was randomised to receive either an UD-BMT or a haplomismatched family donor transplant. Twenty six of the patients received transplants for acute leukaemia in their second or a subsequent remission. All children received intensive conditioning treatment before the transplant, and T cell depleted donor marrow as prophylaxis against graft versus host disease. The length of follow up since the transplant at the time of writing is short, but the projected survival of patients receiving both mismatched family and unrelated grafts two years after bone marrow transplantation was 40–50%.[19] At present most paediatric haemotologists are reluctant to treat patients with acute leukaemia with no particular risk factors with UD-BMT in their first remission because of the relatively good prognosis with chemotherapy alone, or chemotherapy together with an autograft.

SEVERE APLASTIC ANAEMIA

Children with severe aplastic anaemia have a poor outlook if treated with immunosuppressive treatment, especially those children who present under the age of 5, with a neutrophil count before treatment of $<0{\cdot}2\times10^9/l$.[20] It is this severely aplastic group of children who should benefit most from UD-BMT, but at the same time they tolerate the wait for an unrelated donor badly. Often the unrelated donor registries will 'fast lane' a search for a severely aplastic child, with excellent results providing the child does not have an unusual HLA phenotype that slows down the search (J Cornish, personal communication). Results of UD-BMT for severe aplastic anaemia have been poor probably because of the high proportion of sensitised patients with advanced disease who were given transplants.[12] More recently, better results have been documented in a small number of patients who received transplants after an intensive bone marrow transplantation conditioning regimen and T cell depleted donor marrow.[14]

OTHER DISORDERS

At present most paediatric haematologists are reluctant to treat thalassaemia major by UD-BMT because of the relative success of alternative treatments and the increased risk of severe graft versus host disease currently associated with UD-BMT.[21] Another well defined group of children not often considered for UD-BMT are those with congenital immune deficiencies. This is because of the relative success of haplomismatched family donor bone marrow transplantation. The use of family donors has the additional advantage that there is no delay in finding a donor and bone marrow transplantation can be carried out before the child develops overwhelming infection.

The probability of finding a 'matched' unrelated donor

EFFECT OF SIZE OF DONOR POOL

Bradley estimated the probability of finding a HLA-A,B, DR matched, mixed lymphocyte reaction negative donor from different sizes of donor pools.[22] Computer simulated searches were based on the HLA phenotypes found in over 1000 randomly selected kidney donors in the United Kingdom. This pool of HLA phenotypes were used to simulate UD-BMT donor panels of various sizes, and to create an artificial recipient population. It was calculated that on average 43% of potential recipients would be found a HLA-A,B, and DR matched, mixed lymphocyte reaction negative donor from a panel of 100 000 volunteers. The validity of this prediction when used clinically depends on the potential recipients and donors having a predominantly white background.

EFFECT OF ETHNIC MISMATCHING OF POTENTIAL DONORS AND RECIPIENTS

Both theoretical calculations[23] and analysis of unrelated donor searches entered into the IMUST study show that if the potential recipient is not white the probability of finding an HLA matched donor from the existing donor registries (which are predominantly white) is less than 10%.[16] This HLA mismatching between ethnic groups is currently a serious barrier to finding unrelated donors for non-white patients. As discussed above, an extended family donor search may be fruitful for these patients. A future aim is to set up donor panels in countries where large numbers of volunteers from appropriate ethnic groups are available.

BONE MARROW DONORS WORLD WIDE

Van Rood has compiled a directory in collaboration with the major unrelated donor registries called *Bone Marrow Donors Worldwide*. This book is used by national donor registries to locate potential donors in other countries for patients for whom a donor search has failed locally. This book may help locate donors for patients with unusual HLA types, including non-white patients.

The future of unrelated donor transplantation

THE IMUST STUDY

The routine method first established for HLA matching of unrelated donor and recipient pairs was to HLA-A and B type donors at the time they volunteered by routine serological techniques. This was followed by HLA class II typing at the time the donor was found to be HLA-A and B identical with a potential recipient. Initially class II typing was done by serology, but more recently analysis of DNA restriction fragment length polymorphisms (RFLP) or DRB, DQA, and DQB genes[24] has proved to be more versatile and cost effective. By RFLP analysis it is possible to detect HLA class II variants not apparent with serological techniques. Classically the mixed lymphocyte reaction has been used as the final arbiter of whether an unrelated donor is a suitable match for a potential recipient. Experience has shown that this test is cumbersome and technically difficult to interpret as part of an unrelated donor search. It may be possible to improve matching by replacing the mixed lymphocyte reaction with RFLP typing of class II region genes supplemented where necessary with typing with allele specific oligonucleotide probes[25] and isoelectric focusing of HLA class I variants not detectable by serological techniques.[26] These developments would firstly improve the accuracy of HLA typing and secondly speed up the unrelated donor search by eliminating the mixed lymphocyte reaction.

The future of unrelated donor transplantation

THE IMUST STUDY

At present there are no universally accepted guidelines to establish the minimum level of HLA matching required between unrelated donors and their recipients, or clinical guidelines for determining which patients should be considered for UD-BMT. Currently the unrelated donor search and the success of UD-BMT is being prospectively evaluated by the IMUST study group.[9] The main conclusions from this study should be available by 1993. In parallel to the IMUST study, a series of laboratory techniques for HLA typing and matching unrelated donors are being investigated.

UMBILICAL CORD BLOOD TRANSPLANTS

Two problems already clearly defined in UD-BMT are the excessive time taken to find a 'matched' unrelated donor[17] and the high incidence of acute graft versus host disease seen after UD-BMT.[21] Recently Gluckman *et al* reported a successful transplant for Fanconi's anaemia using HLA identical sibling cord blood as the source of haemopoietic progenitors.[27] The number of haemopoietic progenitor cells measured by short term clonogenic assays for granulocyte-monocyte, erythroid, and mixed colony forming units in a single cord blood donation is only slightly lower than the number routinely infused into adult ID-BMT recipients.[28] In the future it may be possible to use a bank of cord blood to solve the logistic problems of unrelated donor searches. Furthermore, there is a theoretical possibility that the fetal lymphocytes present in cord blood donations will have less potential for causing graft versus host disease than adult lymphocytes from marrow donors. This alternative source of haemopoietic progenitor cells is being investigated.

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Breast milk and necrotising enterocolitis

Breast milk protects babies against necrotising enterocolitis. 'I know that', I hear you say. And on what basis do you know that? On the basis of a few inconclusive clinical observations and animal models according to workers at the MRC Dunn Nutrition Unit in Cambridge.

The Cambridge based five centre trial of feeding of low birthweight babies (<1850 g) came up with remarkable results in June 1990 showing that babies fed a preterm formula developed better than those fed on standard formula (see Archivist, November 1990:1265). Now (*Lancet* 1990;**336**:1519–23) they have shown that breast milk has a considerable protective effect against necrotising enterocolitis.

The disease was 6–10 times more common in babies fed exclusively on formula milk than in those given only human milk. It made no difference whether the human milk was fresh mothers' milk or pasteurised donor milk or whether the formula milk was standard or preterm. The benefits of breast feeding have usually been said to be eliminated if complementary formula feeds are given but in this trial babies fed exclusively on formula were three times as likely to get necrotising enterocolitis as those fed on both human and formula milks. Delaying the first feed reduced the incidence of the disease in formula fed babies but not in those given human milk. With increasing gestational age above 28 weeks babies fed formula had a persistently high incidence of necrotising enterocolitis (8–9%) whereas in those given human milk the incidence fell progressively and there were no cases at gestations above 33 weeks. The authors calculate that giving human milk to all low birthweight babies could prevent about 500 cases of necrotising enterocolitis and 100 deaths each year in the United Kingdom.

Human milk is good for premature babies. Preterm formula is good for premature babies. The suggestion is that you can have the best of both worlds by using both.

ARCHIVIST

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ANATOMY OF CHANGE

Low birthweight infants: immediate feeding recalled

Pamela A Davies

The minutiae of low birthweight infant feeding rarely evoke unanimity among paediatricians. What to feed, how much of it to give, how to get it in, and what the long term effects might be, still occasion debate. The question of when to start after birth had its share of controversy nearly 30 years ago, and events leading to a change in practice are described.

The timing of the first feed was last reviewed here in 1978.[1] At the beginning of the century it was felt that feeding should begin as soon as possible after birth to prevent death from inanition. But for Julius Hess, an American physician renowned then for his pioneering care of low birthweight infants in Chicago, and an advocate of an early start, this meant giving nothing for the first 12 hours of life, and one to three feeds of human milk, obtained from a wet nurse if necessary, in the second 12 hours, 'if the infant's condition warrants'.[2] The fear of aspiration of milk into the lungs was great. With feeble or absent sucking and swallowing reflexes in the most immature infants, and the tools for the job confined to spoon, pipette, or fountain pen filler, this is not surprising. However some 27 years later Hess was to counsel that the period of starvation for babies weighing less than 1200 g should be 24–48 hours, subcutaneous injections of physiological saline being given in the interim.[3] Mary Crosse, who started the first 'premature baby unit' in the United Kingdom, also changed her mind. In the first edition of *The Premature Baby*, published in 1945, she advised a 12 hour initial fast with dilute milk delayed to the third or fourth day. In the third, fourth, and fifth editions (the latter published in 1961) she advised that the first 24–96 hours should be without fluid of any kind.[4]

This was despite the fact that feeding techniques were advancing, for oesophageal gavage feeding with rubber tubes had been practised in the 1940s and plastic indwelling nasogastric tubes became available in the early 1950s. And although two voices opposed the prolonged starvation period,[5 6] 'scientific' rather than practical reasons for the delay were appearing. Clement Smith, noted for his work on the physiology of the newborn infant in Boston, Massachusetts, proposed in 1949 that as many low birthweight infants were oedematous and excreted large amounts of urinary sodium and potassium in first days of life, oedema would be increased and prolonged if solutions containing sodium were given.[7] Smith was an influential voice in the United States and United Kingdom. He had persuaded Gaisford and Schofield in Liverpool to impose further extremes of starvation, even up to 111 hours,[8] and at a meeting in Finland disagreed with Yllpö, who believed starved babies became acidotic and should be given 5% glucose solution in the first 24 hours.

Hints of a change in attitude, however, were evident from 1960 onwards. In America Bauman reported a controlled trial in which preterm infants were given either 5% dextrose in 0·45% saline by nasogastric drip starting six hours after birth or nothing until the age of 36 hours, when both groups started milk feeds. Neither beneficial nor detrimental effects were recorded.[9] Smith's group gave the same dextrose saline mixture early (within four hours of birth) to one group of infants of diabetic mothers, another being starved for 48 hours. While the incidence of hyaline membrane disease was unchanged, early feeding reduced indirect bilirubin concentrations, lessening the need for exchange transfusion.[10] And in the United Kingdom Laurance and Hutchinson-Smith also reported less jaundice among preterm infants fed early rather than late with undiluted breast milk.[11] Clement Smith, in his Borden Award address in 1962 considered he had been wrong in 1949 to put oedema forward as a reason for delaying feeding; most preterm infants were not oedematous at birth, though various stresses such as cold might make them so. He believed feeding techniques were improving fast so that aspiration was less common. He still nevertheless felt that the low birthweight infant could manage without added energy initially as he considered the babies had enough stored glycogen and fat, and tissue protein available for catabolism, to prevent them dying of inanition.[12]

Victoria Smallpeice, clinical director of the paediatric department in the United Oxford Hospitals had felt increasingly uneasy about such a practice for some time. She argued that the nourishment afforded the fetus via the placenta was continuous and that it made little sense to stop supplying it abruptly at birth and over the period of highest mortality. She recalled that as a medical student she had been impressed with the then unorthodox views of one of her teachers: he believed the prolonged starvation imposed on patients with typhoid fever was harmful. He had not found that allowing them a relatively liberal diet had influenced the likelihood of perforation and if this did occur they were in much better shape for

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surgery, which previously had a high mortality. She heard the professor of surgery at the Institute of Child Health, London—Andrew Wilkinson—speak at an international congress of paediatrics in Lisbon in 1962 on the metabolic costs of starvation in newborn infants undergoing surgery, and the reparative effect of early feeds of undiluted breast milk on this chemical chaos. This fitted in with McCance's concept of continued growth being all important in the maintenance of normal homoeostasis.[13] These ideas excited her and she returned from the Lisbon meeting resolved to start feeding low birthweight infants very soon after birth with expressed undiluted human milk. Her colleague Hugh Ellis generously allowed all infants weighing 1000–2000 g born in or admitted to the Nuffield Maternity Home at the Radcliffe Infirmary to be under her care for a trial period. This started in November 1962 and continued until the end of March 1964, by which time 111 infants had been included. Eight of the original 119 of the stipulated weight range had to be excluded: two because of oesophageal atresia, one whose admission was delayed until the fourth day, and five during the early part of the trial who died within four hours of birth without being fed.

The babies were fed via an indwelling nasogastric polyvinyl tube and were given 60 ml/kg of undiluted human milk in the first 24 hours of life, 90 ml/kg on the second day, 120 ml/kg on the third, and 150 ml/kg on the fourth. That this break with traditional care was introduced with apparent ease was largely due to the enthusiasm and skill of the young nursing staff. The trial was uncontrolled, but comparison was made with the 45 infants of the same birthweight cared for at the Churchill Hospital, Oxford, over the same time period, by the same medical staff, but fed later. The early fed infants had lower mean serum bilirubin concentrations and passed their first meconium and regained birth weight at earlier mean times (all $p<0{\cdot}05$). Twenty seven of the 111 (24%) early fed infants died, as did 12 of 45 (27%) of the later fed.

The paediatric section of the Royal Society of Medicine held its summer meeting in Oxford in 1964 and these results were reported there.[14] I think it is fair to say they were listened to with some interest, but doubt and scepticism were also evident. The results were later recorded in more detail in the *Lancet*,[15] and a few months later an editorial there adopted a rather lofty tone of disapproval implying that any possible advantages were outweighed by the risks, and that if 'nature' had created the healthy mature human infant to observe 'temperance and moderation' over his first drink, then presumably she also knew best where the preterm infant was concerned.[16] The nature argument did not cut much ice with Smallpeice and Davies who knew that many full term infants would suck avidly at the breast within a short time of birth given the chance, and who felt she was a poor model for the preterm infant, mortality in that situation being nearly 100%. But was the *Lancet* editorial right about the risk? Perinatal mortality for infants weighing 1000–2000 g at the Radcliffe Infirmary was lower in the single full year of the trial (1963) than in any year since records were first available there (1952), but this was not a controlled trial. Towards the end of 1965 Wharton and Bower published the results of such a trial undertaken at the Sorrento Maternity Hospital, Birmingham, the unit from which Mary Crosse had lately retired. A total of 239 infants were involved, alternate admissions being fed within two to eight hours (usually within two to four hours of birth) using volumes similar to those used at Oxford, the remainder being fed at 12 to 16 hours with much smaller amounts. The mortality in the early fed group was 17%, and in the later fed group 6% ($p<0{\cdot}01$). When deaths considered inevitable or 'due to factors other than immediate feeding' were excluded, a substantial difference (13·8% compared with 5·8%) remained but did not reach significance.[17] Wharton and Bower reported that in some very preterm infants in the early fed group 'apnoeic attacks with cyanosis and circulatory failure were regularly occurring after each feed'; six of 20 infants who died in this group were considered to have aspirated feeds. Bilirubin concentrations were significantly lower and birth weight was regained significantly earlier in the immediately fed group ($p<0{\cdot}01$ for both). Symptomatic hypoglycaemia occurred in four of the later fed group, one of whom died, but in none of the early fed group. The authors reported they intended to continue early feeding with undiluted breast milk, but reduce the volumes by a third. In Oxford no change was made.

Appreciation of the concept of intrauterine growth retardation was fast gaining ground, and the tendency of these small for gestational age infants to have low blood glucose concentrations was becoming more widely understood. Experimental work too was suggesting that food restriction at a certain vulnerable period early in life might result in permanent stunting of organ and body size; this in turn being explained by what John Dobbing dubbed the cell number/cell size hypothesis.[18] It engendered a good deal of excitement at the time, particularly with regard to the growing brain, and caught up in this when following up low birthweight infants at Hammersmith Hospital later, I thought their later outcome might give some support for the experimental work.

Infants weighing less than 1500 g at birth cared for there between 1961 and 1964 had been given significantly less food in the first week, and had significantly lower body temperatures for the first four weeks of life than similar infants born in 1965 to 1968.[19] Head circumference centiles of infants appropriately grown for gestational age showed a normal distribution in the latter four years, but were skewed to the left in the earlier period, as were those of small for gestational age infants throughout the entire eight years. This was interpreted thus: lower body temperatures consequent on the lower environmental temperatures imposed during 1961 to 1964 could mean that energy derived from food would have to be diverted to heat production instead of being available for growth, and infants appropriately grown at birth were being converted to growth retarded ones after birth by lack of warmth and food. The results were thought to give some support for the hypothesis that relatively minor undernutrition during a time of very rapid brain growth could result in a deficit in the ultimate size of the brain.

Some years later, but before being aware that the brain does not grow first by cell multiplication to an adult number followed by a later increase in cell size (the cell number/cell size hypothesis[18]), I felt the above conclusions were doubtful. The numbers were relatively small, the infants were cared for before cerebral ultrasonography was being applied in neonatal units, and it seemed probable that not a few of the 'well grown' heads could be associated with ventricular dilatation as survival from intraventricular haemorrhage increased. Thus if there were benefits to be gained from reducing the period of starvation to as short a time as possible I believe they lay more in preventing symptomatic hypoglycaemia, reducing bilirubin concentrations and the need for exchange transfusion, and in allowing somatic growth to resume earlier, than in any important effect on brain growth.

Were there harmful effects of immediate feeding? The increased mortality of the alternate case trial at Birmingham has already been referred to; careful review of the Wharton and Bower paper led us to believe the verdict was not proved. But in any event both trials have been largely overtaken by the increasing survival of very immature babies, and a single regimen of feeding suitable for all low birthweight infants can no longer be prescribed. The larger numbers of infants with birth weights less than 1000 g now surviving was the spur for further research into their nutritional requirements.[20] The skill and care with which young doctors and nurses developed parenteral feeding were in no small measure responsible for lowering mortality. Few would deny that it can occasionally have serious, even lethal, complications but used for short periods in the transitional stage after birth when respiratory illness is most likely it has proved invaluable. I resisted it for too long.

The arrival of numbers of cases of necrotising enterocolitis in neonatal intensive care units some 20 or more years ago gave me considerable concern as I wondered if it could have been associated with immediate and liberal enteral feeding. The condition has been recognised in sporadic case reports since the end of the last century and has now been described in infants never fed or fed only intravenously. Its dramatic impact coincided with a period of rapidly falling mortality among low birthweight infants so that the new breed of very immature, often sick babies were at risk from a condition whose salient features seem to be a disturbance both of the integrity of the intestinal mucosa, and of bowel flora (often altered by antimicrobial drugs), allowing certain bacteria to multiply to critical levels. It is still possible that like its near relative of adult life, pseudomembranous colitis/antibiotic associated diarrhoea, certain bacterial toxins will ultimately be found to have a decisive role. The occasional clustering of cases in neonatal units suggests infection may be important. Early feeding with breast milk as practised by us on balance is unlikely to have been causal. But just as starvation was sometimes carried to extremes, I think it was sometimes followed in the 1970s by a certain immoderate liberality of both enteral and parenteral fluid. For a condition whose aetiology is clearly multifactorial, a cautious graduated approach to total intake in those at particular risk seems wise.

Drillien recorded particularly poor results at follow up of low birthweight children in Edinburgh in two years (1953 and 1954) when fluid had been witheld completely for the first three to four days of life there, milk not being introduced until the fifth to ninth days, a truly spartan regimen.[21] While no one to day would venture feeding breast milk within an hour or two of birth to a 500 g infant, I think it is unlikely that those of low birthweight will ever again be starved as they largely were when Victoria Smallpeice—with vision and not a little courage—inaugurated her trial of early feeding with human milk in 1962. Her belief that their nutrition should be interrupted as briefly as possible so that growth could be resumed soon after birth is likely to endure. If the benefits of her work have been difficult to measure with precision because of a rapidly changing neonatal scene, I do believe them to be real. I was privileged to work with her in those days and learned many lessons from my involvement with early feeding.

Dr Victoria Smallpeice will I hope celebrate her 90th birthday this year. I am greatly indebted to her for going over old ground again with me for this article and for her continuing keen interest in, and critical discussion of matters neonatal since her retirement in 1966.

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PERSONAL PRACTICE

When does an EEG contribute to the management of febrile seizures?

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The above question implies that the electroencephalogram (EEG) can be of some value in the care of children with febrile seizures. Not everyone would agree. For example Aicardi states uncompromisingly that 'EEG tracings are useless as they do not help predict the occurrence of later epilepsy'.[1] Some accounts are so disdainful that they do not mention electroencephalography at all.[2] However other authors are less sure: 'The role of the electroencephalogram in the work-up of febrile seizures remains controversial'.[3]

The possible value of the EEG in these circumstances depends to some extent on the definition of febrile seizures and the possible identification of different types. Both are still contentious issues.

Regarding definition, the National Institutes of Health (NIH) consensus statement excluded seizures with evidence of intracranial infection or a definite cause, and also children with previous non-febrile seizures.[3] Although these criteria are accepted in some child neurology texts (for example, Menkes[4]), other authors point to the difficulties of achieving a strict definition in these terms, for example Brett.[5] Aicardi in particular is critical of the NIH consensus definition: 'The absence of intracranial infection and of recognised acute neurological illness remains an unproved assumption in at least some cases'.[1]

As for subgroups, there is general (though not complete) agreement with the distinction made by Livingstone between 'simple febrile convulsions' and 'epileptic seizures precipitated by fever' or 'atypical febrile convulsions' which are also sometimes called 'complex' or 'complicated' febrile seizures.[6] In Livingstone's account simple febrile seizures, accounting for 97% of the total, were brief generalised seizures in children with a family history of febrile seizures, in contrast to atypical febrile seizures that were usually prolonged and often focal or lateralised. Only 3% of the former group developed later afebrile seizures compared with 93% of the latter group. In more recent years it has been claimed that this poor prognosis group is further characterised by such features as neurological or developmental abnormality before the onset of seizures, onset under the age of 1 year, and frequent or prolonged febrile seizures.

These descriptions begin to suggest a possible role for electroencephalography in helping to identify the nature of underlying cerebral pathology in children assigned to the atypical group. However Livingstone's neat distinction between simple and atypical febrile seizures has also been challenged, again perhaps particularly by Aicardi who asserts that although a large majority of simple febrile seizures are brief, bilateral and benign in outcome, some children have a combination of simple febrile seizures and long lasting unilateral seizures in spite of a strong family history of febrile seizures.[1] Chevrie and Aicardi point out that even some febrile seizures with residual neurological signs are not necessarily followed by epilepsy.[7] In addition the severity of the attacks may not be a good predictor of outcome as almost 90% of patients who develop epilepsy have had only brief bilateral seizures.[8] In a later publication Aicardi and Chevrie concluded that unilateral, prolonged febrile seizures are a heterogeneous group containing some children who have seizures because of genetic vulnerability to fever but also others who convulse because of acquired brain injury.[9] Aicardi concludes: 'simple seizures—defined as brief, bilateral attacks in previously normal children—are not necessarily true febrile convulsions, in the sense of seizures entirely resulting from an abnormal constitutional response to fever.[1] Conversely, complex febrile convulsions or febrile statuses can be true febrile convulsions, . . . the complete separation between simple and atypical febrile convulsions reported by Livingstone has not been confirmed in any other series'. This view should not be construed as excluding the possibility of defining in the future convincing subgroups of children with febrile seizures. Indeed, for example, Aicardi himself points out that febrile seizures of early onset and long duration with only a low grade fever and a positive response to photic stimulation on electroencephalography can be the first manifestation of 'severe myoclonic epilepsy of infants'[1].[10]

Reports of EEG abnormalities in children with febrile seizures (table)

(1) Ictal EEGs

Recordings during acute febrile illness with seizures have rarely been reported. They can be expected to show generalised rapid spiking as in any tonic or tonic-clonic seizure but according to Lennox-Buchtal some show severe lateralised electroencephalographic changes of this type.[11] In her study, however, no distinction was made between simple and atypical febrile seizures.

EEG abnormalities in children with a history of febrile seizures

Ictal (rarely reported)	Generalised spiking Lateralised spike wave discharge
Postictal	Slow activity Spike wave or spikes
Serial EEGs	Bisynchronous theta activity Bisynchronous spike wave at rest and during overbreathing Bisynchronous spike wave on photic stimulation Focal spikes or sharp waves Hypnagogic paroxysmal spike wave

(2) Postictal EEGs

(a) Recordings taken on the same day as the seizure have been reported to contain slow activity in as many of 88% of cases. The same type of abnormality is described in about a third of children between three and seven days after a seizure.[12] This slow activity is predominantly posterior in distribution and, although mostly bilateral, is often asymmetrical or even unilateral. It tends to resolve over about a week. The reports by Pampiglione[13] and Wallace and Zealley[14] suggested that such abnormalities can be expected in association with viral illnesses whether or not seizures occur, although not in relation to changes of temperature.[15] However Rantala *et al* found no difference in the early electroencephalographic findings (including the presence of abnormal slow activity as well as spikes or sharp waves) between those with and those without a proved viral infection.[16]

(b) Spikes or spike and wave discharges, localised or generalised, are rare in the early postictal period. Frantzen *et al* gave a figure of 1·4%[12] and Kajitani *et al* suggest 3%.[17] Both these figures are close to the 1·9% given by Eeg-Olofsson[18] as the incidence of focal sharp activity in normal young children.

Rantala *et al* suggest that the presence of any of these abnormalities does not distinguish between simple febrile seizures (defined in their study as lasting less than 15 minutes and without focal features) and complicated febrile seizures (that is, lasting longer than 15 minutes, with focal features or recurrence within 24 hours).[16] In this investigation febrile seizures were defined as a first seizure associated with fever irrespective of age and excluding children with earlier non-febrile seizures, evidence of a brain infection or metabolic encephalopathy.

(3) Serial EEGs over several years

Frantzen *et al* reported that 29% of children showed some form of 'epileptic' activity in the few years after their last febrile seizure.[12] Doose *et al* carried out a longer electroencephalographic follow up study on children with febrile seizures to the age of 11 to 13 years and reported that 81% had abnormal EEG patterns.[19]

These authors described three types of abnormality all considered to represent genetically determined patterns: (a) bilaterally synchronous and regular 4–7 cycles per second (theta) rhythms seen mainly in parietal regions occurring in 54% of his series of children with febrile seizures. (b) Generalised spike wave discharge occurring in the resting EEG or in response to overbreathing. This pattern was seen in 49% with age of onset usually between 3 and 6 years. (c) Generalised spike wave in response to photic stimulation was seen in 42% mainly in children under the age of 5 years.

From this and other reports it appears that generalised spike wave discharge is unusual at the younger age for febrile seizures (that is, under 2 years) appearing on average about sixteen months after the first febrile seizure up to as late as four years after it.[11 20] The discharges can be intermittent with sometimes months or years apparently in abeyance, although the sampling error of repeated brief electroencephalographic recordings has to be remembered.

Focal spike or sharp wave discharges have been reported in between 8% and 10% especially where a persistent slow have focus was seen previously usually after a prolonged seizure.[1] However, such discharges are also seen after brief febrile convulsions, looking very much like centrotemporal spikes of later childhood.[21] Kajitani *et al* reported this finding in 4·2% of children on follow up.[17]

Another obvious abnormality in the later EEGs of children with febrile seizures is that described by Alvarez *et al*.[22] They emphasised the occurrence of generalised, paroxysmal, high amplitude rhythmic 3–5 cycles per second slow activity with intermixed spikes in drowsiness ('hypnagogic paroxysmal spike wave activity' or 'hypnagogic PSW') in perhaps a quarter of children with febrile seizures, mainly in the second year of life and rarely younger than this. This feature was not seen in a group of normal controls and appeared in only 9% of a group of children referred for electroencephalography for neurological problems but without febrile seizures. There appeared to be no clinical difference between children in the febrile seizure group with or without the EEG abnormality.

Prospective studies

These various abnormalities are very interesting but there seems to be universal agreement that none of them bears any convincing association with the eventual development of epilepsy (that is, recurrent afebrile seizures of primarily cerebral origin) in these children. Some key studies of febrile convulsions concerned with risk factors for later afebrile seizures did not specifically assess the role of electroencephalography.[23 24] However the discussion in the NIH consensus statement on febrile seizures is instructive on this point.[25] The discussion started with the assertion that on general principles electroencephalography findings ought to be predictive of later epilepsy and therefore should form one of the considerations on which each child's management should be based. However, a series of studies were than quoted by Hauser (USA), Thorn (Denmark), and Camfield (Canada) all of which indicated no association between early electroencephalography findings and later seizures. Incidentally, these general conclusions seem to apply to boys and girls equally.

Conclusions concerning the clinical value of EEG investigations in children with febrile seizures

Clinical value

An early postictal standard EEG will not be helpful in the following respects: (a) it will not distinguish between clinically simple and atypical seizures and (b) it will not particularly help in the identification of a cerebral infective aetiology. (c) EEG findings lack predictive value for the later occurrence of either further febrile or later afebrile seizures. As Aicardi says, epileptic activity will be found in a high proportion of older children who are less likely to develop recurrent seizures and later epilepsy, whereas they will almost never appear in the EEGs of young infants that are at maximum risk of recurrence, later afebrile seizures, and severe febrile seizures.[1] It is these discrepancies that lead Camfield to say in the above NIH discussion that 'It makes more trouble than it is worth' to carry out recordings in these circumstances; 'you wish you had not done the EEG', because with an abnormal result discussions with parents about its significance can be very difficult. For these reasons electroencephalography cannot be recommended as a routine measure in children with a febrile seizure.

Perhaps, however, there is a limited place for electroencephalographic studies in connection with febrile seizures in those cases where there is clinical reason to suspect cerebral pathology. If the child showed developmental delay or other evidence of neurological impairment before the occurrence of the febrile seizures, or if the first seizure occurs below the age of 12 months, or if the seizures contain partial (focal) features in the ictal or postictal phase, it seems prudent to consider the possibility that the child's seizures may be evidence of brain pathology, perhaps structural. From the above account it is clear that these clinical features do not necessarily suggest a brain lesion and in most cases the findings on further investigation will be normal, but in some instances they will be found to indicate a significant brain abnormality.

In addition, if a child has suffered a prolonged febrile seizure, especially if it is followed by residual neurological signs or developmental regression, the possibility of structural change caused by the convulsions needs to be considered and investigated in a similar way in view of the evidence that various degrees of brain damage can be sustained during the course of a prolonged febrile seizure.[9]

Electroencephalography is not the investigation of choice in considering structural pathology and computed tomography or magnetic resonance imaging would be more appropriate. It can be a useful ancillary investigation capable of suggesting persistent brain pathology (even in the presence of a normal computed tomogram) if it demonstrates an abnormality (usually irregular slow wave disturbance with or without associated spike or sharp wave discharges) which is persistent. Clearly this implies the use of serial EEG recordings perhaps over a period of weeks rather than a single recording.

Although not immediately relevant to the management of children with febrile seizures, the high rate of the various EEG abnormalities mentioned earlier (including the different forms of seizure activity) on long term serial electroencephalographic follow up of children with febrile seizures, means that there is a serious risk of misdiagnosing epilepsy on the basis of such EEG findings alone. Seizure discharge found incidentally in older children should not necessarily be construed as evidence of current epilepsy. Especially in the presence of a history of febrile seizures, such abnormalities may well be simply evidence of a persistent genetically determined electroencephalographic trait unassociated with the risk of afebrile seizures.

Research

Another possible although very different place for electroencephalographic investigations in children with febrile seizures concerns research, especially the investigation of genetic factors. The morphological similarity mentioned earlier between some of the focal spike or spike wave discharges seen in some children years after the febrile seizures and the centrotemporal spike discharges in benign rolandic epilepsy of childhood has led to the suggestion that there may be some genetic connection between febrile seizures and this form of epilepsy.[17] Similarly Doose *et al* have suggested that various genetically determined EEG patterns can be found in a high proportion of patients with febrile seizures, that is, biparietal theta rhythms, spike wave activity in the resting state and on overbreathing, and that provoked by photosensitivity as described earlier.[19] Alvarez *et al* suggested that hypnagogic paroxysmal spike wave is also a genetically transmitted EEG pattern.[22]

Genetic studies are not the only type of research needed in the field of febrile seizures. The possibility of defining clinically important subgroups was mentioned earlier in connection with severe myoclonic epilepsy of infants.

Whatever aspect of febrile seizures is researched, as Alvarez and his colleagues rightly point out,[22] published studies contain clear inconsistencies not only in the criteria used to compare patient groups in different studies of febrile seizures, but in the way electroencephalographic information has been obtained. They are right to recommend, certainly for research purposes, that recordings should be concerned with natural sleep and wakefulness, drowsiness, at least stages 1 and 2 of non-rapid eye movement sleep, arousal, and wakefulness. Failure to standardise the procedure makes comparisons between different studies very difficult. Certainly if this sequence is not followed there will be a failure to demonstrate not only hypnagogic paroxysmal spike wave but other spike wave discharges during sleep with which hypnagogic paroxysmal spike wave might be confused.

Further exploration of these possibilites dependent on electroencephalographic studies would be interesting and justified within the confines of a specific research protocol. Outside the circumscribed clinical and research settings just mentioned electroencephalographic investigations of children with febrile seizures cannot be recommended.

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5 Brett EM. *Paediatric neurology*. Edinburgh: Churchill Livingstone, 1983.

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12 Frantzen E, Lennox-Buchtal MA, Nygaard A. Longitudinal EEG and clinical study of children with febrile convulsions. *Electroencephalogr Clin Neurophysiol* 1968;**24**:197–212.

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15 Minchom PE, Wallace S. Febrile convulsions: electroencephalographic changes related to rectal temperature. *Arch Dis Child* 1984;**59**:371–3.

16 Rantala H, Uhari M, Tuokko H. Viral infections and recurrences of febrile convulsions. *J Pediatr* 1990;**116**: 95–159.

17 Kajitani T, Ueoka K, Nakamura M, Kumanomidou Y. Febrile convulsions and rolandic discharges. *Brain Dev* 1981;**3**:351–9.

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21 Heijbel J, Blom S, Bergfors PG. Benign epilepsy of children with centrotemporal EEG foci. A study of incidence in outpatient care. *Epilepsia* 1975;**16**:657–64.

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SISTER JOURNALS—POLAND

Pediatria Polska

The editor and his board are to be congratulated for producing this new volume (with some help from a Western sponsor) of the journal of the Polish Paediatric Association after a long absence due to the difficult economic conditions in which eastern Europe finds itself today. The quality of the production and the variety and substance of the papers augurs well for the future of Polish paediatrics.

The volume of 100 pages contains a number of original papers (alas some submitted as long ago as two to three years), a handful of interesting case reports, a couple of reviews dealing with the use of corticosteroids in allergic disorders and the significance of virus infections in the pathogenesis of asthma respectively, and finally the journal ends with a report of an international meeting on the 'Rights of Children' and a brief historical summary of the development of oncological services for children in Poland.

The British paediatrician would not find a great deal to interest him/her—most of the articles are 'common or garden' stuff here. Possibly the best paper came from a dental faculty in Lublin, eastern Poland and dealt with the development of dental caries in insulin dependent diabetic children and controls, and which concluded that there were no significant differences in dentition in the two groups.

Surprisingly, many references are from English speaking countries, but regretfully most are outdated and from publications that are used in meeting sponsorships in the West. The attempts at brief summaries of the papers in the English language are, to put it charitably—awful and grossly inaccurate. It might be wise for the editors to consider writing in good English a detailed resume of one or two papers which they think may be of interest to the English speaking readers and confine the other submissions to English titles only.

Obviously this journal has taken first brave steps and has a long way to go in order to catch up with the publications in the West. Nonetheless, it was heartening to see so many submissions from various parts of Poland—a clear sign that the editors will not be short of clinical material in the future.

J A KUZEMKO

LETTERS TO THE EDITOR

Hearing screening in children—state of the art(s)

SIR,—Haggard emphasised the extreme importance of early identification of hearing impairment in infants at risk of sensorineural hearing loss and advised evoked response audiometry as a sensitive and specific determinant.[1] Reardon and Pembrey, in the same edition of the journal, documented that 30% of all genetically determined deafness occurs in syndromic form.[2]

Anatomical abnormalities of the inner ear and middle ear are well recognised in association with the head and neck syndromes and at present, imaging of the middle and inner ear is not routinely performed. Although screening tests would detect those infants with hearing impairment, for children with head and neck syndromes or external ear deformities it can only be complementary to imaging, which is the most important investigation, particularly for children in whom improvement is possible by surgical intervention. We believe that for all infants with syndromes associated with ear abnormalities—for example, Klippel-Feil, Treacher Collins, craniofacial microsomia, Wildervanck, Goldenhar, X linked deafness—or for infants with external ear deformities, that conventional tomography or high resolution fine section computed tomography in the neonatal period is essential, and that evoked response audiometry and tomography are complementary procedures.[3]

We have previously reported our series of 17 patients with Klippel-Feil syndrome who underwent hypocycloidal polytomography and axial computed tomography and in whom we found a high proportion of severe inner and middle ear abnormalities, many of which were incompatible with any degree of hearing (RR Phillips, PD Phelps, paper presented at the 50th annual meeting, Royal College of Radiologists, Liverpool 1989). In the inner ear there was a range of abnormalities, the most severe including dysplasia of the bony spiral of the cochlea (known as the Mondini defect), which occurred in six of our patients, or absence of any recognisable cochlear structure (the Michel deformity), which we demonstrated in five patients. There was a range of severity of middle ear abnormalities, which included abnormal ossicles in six patients, absent oval window in two, and small or slit attic in two.

Severe cochlear abnormalities are incompatible with auditory function and therefore bilateral abnormalities imply that education must use methods not involving sound. The Mondini defect allows some degree of cochlear function. For some patients with conductive deafness, surgical correction of the structural abnormalities may be successful in providing a degree of auditory function.

The radiological assessment of congenital deafness must assess inner ear structure, cochlear function, and the risk of cerebrospinal fluid fistula due to structural abnormalities. In the middle ear it must assess the feasibility of surgery for better sound conduction and the presence of any surgical hazards—for example, high jugular bulb. Any deformity of the bony labyrinth indicates a severe degree of sensorineural deafness and is therefore a relative contraindication to surgical attempts to improve the sound conduction mechanism.

Thus in patients with head and neck syndromes or external ear deformities, the early radiological assessment of the inner and middle ears (by conventional imaging and computed tomography in the neonatal period) is essential in order that the range of structural abnormalities may be demonstrated. At this stage imaging may be performed with little, if any, sedation and with a minimal radiation dose. Guidance may then be given regarding the possibility of corrective middle ear surgery and to allow the best methods of communication to be taught from the earliest opportunity.

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1 Haggard MP. Hearing screening in children—state of the art(s). *Arch Dis Child* 1990;65: 1193–5.
2 Reardon W, Pembrey M. The genetics of deafness. *Arch Dis Child* 1990;65:1196–7.
3 Lund VJ, Phelps PD and Beagley HA. Evoked response audiometry and tomography—complementary procedures for the assessment of the deaf infant. *Int J Pediatr Otorhinolaryngol* 1982;4:95–106.

Management of gastroenteritis

Sir,—Professor Walker-Smith's recommendations on the dietary management of infantile gastroenteritis are commendably clear.[1] Unfortunately they do not correspond to the advice in the accompanying article by Jenkins and Ansari, which takes general practitioners to task for 'inappropriately' continuing milk feeds (this category contributed half of the inappropriate management total).[2] Before we chide primary care doctors for their deficiencies we should examine the consistency of our own advice. Official WHO guidance on diarrhoea management is to continue feeding in a breast fed baby, and for bottle fed infants to continue the usual formula every three hours (except during the three to six hour rehydration period),[3] yet paediatricians and major textbooks commonly advise the withdrawal of milk feeds and food for a temporary period.

It is, therefore, hardly surprising that general practitioners do not show a uniform approach. In addition, none of the three papers about gastroenteritis management in the same issue give clear guidance as to whether solid foods should be stopped. Jenkins and Ansari indicate that normal diet should be ceased for 24 hours, but say that this regimen is under debate. WHO advice is that 'food intake should *never* be restricted during or following diarrhoea'.[3]

It is time that our own guidance is brought in line with that adopted in developing countries, and we recommend continued milk and solid feeding in the outpatient management of gastroenteritis.

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1 Walker-Smith JA. Management of infantile gastroenteritis. *Arch Dis Child* 1990;65:917–8.
2 Jenkins HR, Ansari BM. Management of gastroenteritis. *Arch Dis Child* 1990;65:939–41.
3 World Health Organisation. *Programme for the control of diarrhoeal diseases. A manual for the treatment of diarrhoea.* Geneva: WHO, 1990.

Professor Walker-Smith comments:

It is certainly difficult for general practitioners to have a uniform approach when there is at present no general agreement among paediatricians concerning dietary management of gastroenteritis in infancy. Dr Waterston cites WHO advice that has been aimed at developing communities. In such communities nutritional status is often already seriously compromised whereas in developed communities it is usually not. Furthermore gastroenteritis is usually less severe in the latter. While there is general agreement that breast feeding should continue in infants who develop gastroenteritis with additional oral rehydration therapy as appropriate, there is no such general agreement about bottle feeding. There is, for example, no satisfactory published study from the UK comparing the regimen of 24 hours oral rehydration solution alone and no feeding to a regimen where bottle feeding is continued unrestricted. Whereas there are studies to show that after such a 24 hour period there is no advantage for regrading rather than returning to full strength feeds. Until such a study is published most paediatricians would agree with Jenkins and Ansari, that in this country the normal diet should cease for 24 hours. They are correct to say that this regimen is under debate.

Drs Jenkins and Ansari comment:

We thank Dr Waterston for highlighting an important area that needs clarification. We would wish to remind him that, at the time we carried out our study, the recommendations regarding the dietary management of gastroenteritis in the UK were clear and unequivocal and were published by Professor Walker-Smith and his colleagues.[1] However, as we clearly stated in our paper, the guidelines may well require updating in the light of further experience. We fully endorse the WHO guidelines (1990) for the developing world where cessation of feeding may mean the difference between life and death, although these guidelines are not necessarily appropriate for the developed world where the disease is relatively mild. Until clear evidence is available from controlled studies that similar guidelines are to be recommended for the UK we will continue our present practice of providing oral rehydration solution and stopping milk feeds and solids for a period of time (6–24 hours) after which full strength feeds and solids may be restarted.

1 Wharton BA, Pugh RE, Taitz LS, Walker-Smith JA, Booth IW. Dietary management of gastroenteritis in Britain. *BMJ* 1988;296:450–2.

Drs Mandal and Dunbar comment:

Dr Waterston has taken us to task for our failure to give clear guidance to general practitioners on whether solid foods should be stopped temporarily during the initial phase of gastroenteritis management. However, our paper was not about the general aspect of management of gastroenteritis. We were looking at a very specific issue—that is, whether the currently widely given advice on graded reintroduction of an infant's usual feeds are necessary for children below the age of 6 months. Thus our study was specifically designed to establish whether there is any advantage in such regrading, with particular reference to recurrence of diarrhoea, effect on weight, and duration of hospital stay. We did not find any advantage in the traditional approach of regrading patients below the age of 6 months with gastroenteritis. We also found that children with lactose intolerance can be satisfactorily managed with a lactose free soy based preparation. Professor Walker-Smith has expressed reservation about this approach because of the risk of soy protein allergy but the incidence of soy intolerance has been no more than 1% or so in our unit despite its use over many years.

We do not accept that there has been any confusion over the advice given to British doctors over the general management of gastroenteritis. The recommendations on the dietary management of gastroenteritis have always included withdrawal of the infant's usual formula feeds and solids and their replacement with an oral rehydration solution for 24 hours after which the feeds should be reintroduced. In developing countries where multiple attacks of gastroenteritis are common, often leading to malnutrition, continued milk and solid feeding has been practised with no apparent ill effects, but as in the case of what is the most appropriate sodium concentration and carbohydrate content for the use in developed countries, this also needs to be examined in properly designed studies before there is uncritical adoption of continued milk and solid feeding approach in the management of gastoenteritis in Great Britain.

Helicobacter pylori

Sir,—The regular review on *Helicobacter pylori* makes interesting reading.[1] However the treatment recommended for duodenal ulcer disease is confusing. Colloidal bismuth subcitrate is no longer recommended in either the *British National Formulary* (September 1990) or the manufacturer's data sheet for use in children.

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1 Drumm B. Helicobacter pylori. *Arch Dis Child* 1990;65:1278–82.

Professor Drumm comments:

Dr Campbell's letter highlights a major area of confusion in relation to the treatment of gastritis and duodenal ulcer disease using bismuth containing compounds. It is true that the *British National Formulary* and the manufacturer's data sheet do not recommend colloidal bismuth subcitrate for use in children. The formulary requires that pharmacokinetic data for children must be available if the drug is to be recommended for use in this age group. This information is not available.

There is, however, no evidence that bismuth subcitrate has adverse effects in children other than those already described in adults. These include encephalopathy, which is reversible after withdrawal of the drug, and acute renal impairment after ingestion of an overdose of this drug.[1 2]

Colloidal bismuth subcitrate is certainly not contraindicated in children. A more significant risk during the treatment of *Helicobacter pylori* gastritis may be the development of pseudomembranous colitis as a result of the use of an antibiotic in the treatment regime. We, and others, as noted in the review, have used bismuth preparations in children. Adverse reactions to bismuth used in the treatment of *H pylori* associated gastritis have not been reported in the studies published to date.

1 Hudson M, Ashley N, Mowat G. Reversible toxicity in poisoning with colloidal bismuth subcitrate. *BMJ* 1989;299:159.
2 Taylor EG, Klenerman P. Acute renal failure after colloidal bismuth subcitrate overdose. *Lancet* 1990;335:670–1.

A clinical trial of two parenteral nutrition solutions in neonates

Sir,—Professor McIntosh and Dr Mitchell, while hypothesising that the use of Vamin 9 for parenterally fed preterm infants may have contributed to death through high plasma concentrations of aromatic amino acids,[1] have also illustrated some of the difficulties in attempting comparisons of different amino acid solutions.

We have previously drawn attention to abnormal plasma amino acid profiles in Vamin 9 fed infants.[2] We considered this to be a reflection of the amino acid composition of Vamin 9 rather than an idiosyncratic reaction, as the pattern recurred consistently, and was much less evident when a modified solution containing less phenylalanine was used.[3] One factor which McIntosh and Mitchell do not address in detail, but which may have considerable influence on plasma amino acid profiles, is the amount of enteral nutrition being given. In our original index case of hyperphenylalaninaemia,[2] small volumes of breast milk given as a supplement to parenteral nutrition produced large changes in plasma phenylalanine. The patients of McIntosh and Mitchell received either breast milk or preterm formula in addition to their intravenous nutrition. In fact, by day 5 of the study, the only day during parenteral nutrition on which plasma amino acid profiles were measured, the figures given for mean enteral feed in both infants receiving Vamin 9 and those fed with MB233G represent approximately 60% of the total nitrogen intake. It is therefore difficult to see how valid conclusions can be drawn about the suitability of either amino acid solution as a parenteral nitrogen source.

Although 68 patients were recruited to the study, some died, some were excluded, and some had inadequate blood sampling or blood taken on the wrong day. As a result, the data derive solely from a single plasma amino acid analysis, performed on only seven patients in the Vamin 9 group and five in the MB233G group. Moreover, individual amino acid concentrations are reported as mean (SD) suggesting normal distribution of data. However, the fact that −2SD would give a negative value for 50% of the amino acids measured indicates non-parametric distribution of results, consistent with similar studies.[3] It would therefore be interesting to be able to compare mean (after log transformation to 'normalise' the data) and ranges of individual amino acids.

Finally, single measurements of plasma amino acid profiles may not allow adequate comparison of different solutions as plasma concentrations can vary considerably. This is illustrated by the following plasma concentrations of phenylalanine and tyrosine measured every two weeks in a child with gastroschisis receiving total parenteral nutrition with a constant nitrogen intake: phenylalanine 149, 500, 200, 49, 63, 983, and 260 μmol/l and tyrosine 95, 60, 80, 58, 86, 86, and 145 μmol/l.

The theoretical basis for the formulation of MB233G is of interest, but it remains to be seen whether or not this new solution offers any advantages over alternative preparations.

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1 McIntosh N, Mitchell V. A clinical trial of two parenteral nutrition solutions in neonates. *Arch Dis Child* 1990;65:692–9.
2 Puntis JWL, Edwards MA, Green A, Morgan I, Booth IW, Ball PA. Hyperphenylalaninaemia in parenterally fed newborn babies. *Lancet* 1986;ii:1105–6.
3 Puntis JWL, Ball PA, Preece MA, Green A, Brown GA, Booth IW. Egg and breast milk based nitrogen sources compared. *Arch Dis Child* 1989;64:1472–7.

Professor McIntosh comments:
Drs Puntis and Booth suggest that the enteral component of nutrition may be important in the development of hyperphenylalaninaemia. They point out that on day 5 both groups of infants in our study received approximately 60% of their nitrogen intake enterally. We agree with this, as at this time the intravenous nitrogen intake was about 40% of the total! The point of difference in our two groups was the composition of the intravenous amino acid mixtures and it would seem therefore to be a 'non-sequitur' to suggest the high concentrations of phenylalanine, tyrosine, serine, proline, and asparagine were due to the enteral intake.

There were in fact 16 and 14 patients with 'good' samples for amino acid analysis taken on day 5—see original table 5. We accept that the results were not in a Gaussian distribution—this is why Wilcoxon's signed rank test was used when comparing amino acid concentrations the two groups.

We note the information in the last paragraph which we find very interesting.

We believe that the apparent ability of babies given MB233 to keep their plasma aminogram in the reference range of cord blood aminograms makes it an attractive alternative to Vamin 9 glucose where the aminograms at five days approached the values of infants with untreated phenylketonuria and hereditary tyrosinaemia.

Virological investigations of acute encephalopathy in India

Sɪʀ,—Rabies should be considered in the differential diagnosis of acute encephalopathy in children living in endemic areas. It may present as a non-specific encephalitis without the pathognomonic features such as hydrophobia and a clear history of exposure is not always present. It was therefore surprising that it received no mention in the series of Kumar *et al*[1]—could it have accounted for some of the cases among the 40% in whom they found no cause?

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1 Kumar R, Mathur A, Kumar A, Sethi GD, Sharma S, Chaturvedi UC. Virological investigations of acute encephalopathy in India. *Arch Dis Child* 1990;65:1227–30.

Dr Kumar comments:
Rabies is endemic in the Indian subcontinent. It produces an acute encephalitic illness usually with a pronounced psychological component. We agree that occasionally none of these pathognomonic features may be found and therefore it may account for a few of the fatal 'unexplained encephalopathies' in this study. Although we have discussed other viral encephitides as a cause in this group we have not specifically mentioned rabies. We therefore appreciate Dr Hall's comment.

Sɪʀ,—Dr Kumar and his colleagues in reporting their investigations into the cause of acute encephalopathy in children in Lucknow have not considered the possibility of cerebral cysticercosis in their differential diagnosis.[1]

Cysticercosis in India is not uncommon[2] and parenchymal involvement, the most common form in children,[3] may present acutely. Acute diffuse parenchymatous disease presents with generalised cerebral oedema often severe enough to cause an acute rise in intracranial pressure with deterioration of consciousness and cerebral shifts. Acute focal parenchymal disease presents with localised patchy oedema often resulting in convulsions.

The diagnosis of cerebral cysticercosis may present difficulties. Serology is beset with the problems of poor sensitivity and specificity and cerebrospinal fluid changes are often non-specific and non-diagnostic. Computed tomography has improved diagnostic accuracy but it not always readily available in India. Where there has been the opportunity to perform enhanced computed tomography on Indian patients presenting with seizures, lesions suggestive of cysticercosis have been reported in 26% of cases,[4] excision biopsy confirming the diagnosis in a further series of cases.[5]

A diagnosis of cerebral cysticercosis should be considered in all children presenting with 'acute encephalopathy' in India.

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Auditing community screening for undescended testes

Sɪʀ,—With interest we read the article of Tamhne *et al* about the screening for undescended testes. We were surprised by reported high cumulative rates of orchidopexy especially as the authors state that some of the children in the younger cohort would not have their undescended testes detected and operated on.[1]

In The Netherlands during the period from 1976 to 1986 about 3% of boys between the ages of 0 and 14 underwent orchidopexy.[2 3] Because this percentage is higher than the generally accepted estimate of the prevalence of truly non-descended testes (about 1%[4]) we are making efforts to reduce unnecessary orchidopexy.

As we have reason to believe that in the past the high orchidopexy frequency was related to inaccurate registration of the testes localisation, in some parts of The Netherlands a card for the testes registration was introduced. On this card the localisation of the testes is registered by the person who assists the delivery. If the testes are not scrotal at birth the boys are followed up. After introduction of this card in one region the number of operations for orchidopexy was reduced to an acceptable level.[3]

We chose registration soon after birth because the cremaster reflex is still absent at that time. Because of this reflex we doubt the efficacy of screening boys for undescended testes at 1 year and at school entry. The figures from Tamhne *et al* confirm our opinion that too many boys will be operated on unnecessarily because of retractility of the testes.

In 1989 a retrospective cohort study concerning the localisation of the testes from birth until puberty of 853 boys born in 1973 and living in West Friesland (The Netherlands) was done. In this study, which has been submitted for publication, we found a considerable number of boys with one or two undescended testes, that when previously measured, had been registered as scrotal. In all these boys the testes had assumed a normal scrotal position at puberty. This supports our advice that if the testes were descended no further screenings are necessary.

We agree with Tamhne *et al* that there is a need to set clear guidelines for the diagnosis of undescended testes and for referral pathways. This is important especially to prevent unnecessary operations.

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1 Tamhne RC, Jarvis SN, Waterston AJR. Auditing community screening for undescended testes. *Arch Dis Child* 1990;65:888–90.
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Revised criteria for diagnosis of coeliac disease and medical audit

SIR,—In the recently published revised criteria from the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) for the diagnosis of coeliac disease,[1] emphasis has shifted from the need for repeated biopsies to the response to dietary gluten withdrawal, combined with initial histological appearance of the jejunal biopsy.

It might be thought that this could decrease the use of this unpleasant and time consuming diagnostic procedure. However this may not be the case.

As part of a medical audit programme the clinical and histological details of jejunal biopsies performed in the Royal Liverpool Children's Hospital between January and May 1990 were reviewed.

Analysis of the data showed: (1) Out of 46 attempted biopsies, 10 were initially unsuccessful. (2) Of the 36 children biopsied, only four biopsies were performed after a gluten challenge, the rest were for initial diagnosis. (3) The number of jejunal biopsies for the first five months of 1990 was similar to the whole of 1989 (36 *v* 39) yet proportionately more children started a gluten free diet (11/36 (30%) *v* 10/39 (25%)). (4) Children referred from an outlying hospital were more likely to have a biopsy specimen compatible with coeliac disease (50% *v* 25%). (5) Eleven children commenced a gluten free diet, but only six had the characteristic 'flat' small intestinal mucosa of coeliac disease.

It was concluded that: (1) There was a significant chance of procedural failure with jejunal biopsy in children. (2) Few biopsies were performed after gluten challenge indicating that the practice of diagnosing coeliac disease by repeated biopsies had already lapsed.[2] (3) The increased number of biopsies in 1990 reflected a more aggressive diagnostic approach. (4) Gluten free diet was often commenced in the absence of characteristic histological criteria. With the new criteria these children would require gluten challenge.

It is therefore to be hoped that the use of the revised ESPGAN criteria will reduce dependency upon multiple jejunal biopsies and the inappropriate use of gluten free diet as highlighted by our medical audit.

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1 Report of the Working Group of the ESPGAN. Revised criteria for the diagnosis of coeliac disease. *Arch Dis Child* 1990;65:909–11.
2 Meeuwisse GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;59:461–3.

Crohn's disease

SIR,—Dr Puntis and colleagues have reported in this journal the first case of granulomatous lung involvement in a child with Crohn's disease.[1] It is clear from many previous reports that pulmonary involvement is actually common in chronic inflammatory bowel disease, although only a minority of patients have symptoms or overt signs. Bonniere and colleagues have demonstrated, in 22 adults with Crohn' disease who had no pulmonary symptoms, reduced serum activity of angiotensin converting enzyme, lymphocytosis on bronchoalveolar lavage, increased superoxide anion production from activated alveolar macrophages, and abnormal pulmonary function tests.[2] They concluded that most patients with Crohn's disease have latent pulmonary involvement. After recent findings in this unit, we are now able to suggest a mechanism for this previously unexplained phenomenon.

We have demonstrated production of the cytokine tumour necrosis factor-α (TNF-α) by single macrophages in colonic biopsies from patients with both Crohn's disease and ulcerative colitis,[3] and have found raised serum concentrations of TNF-α in patients with relapsed colonic disease[4]: we consider that chronic TNF-α elevation may contribute to anorexia and growth failure. TNF-α has also been implicated in granuloma formation[5]: granuloma epithelioid cells are in fact activated and transformed macrophages. TNF-α mRNA was found in large quantities within these experimentally induced hepatic granulomas and anti-TNF-α monoclonal antibodies caused both rapid granuloma regression and reduction of TNF-α mRNA content.

TNF-α production is actually increased by exposure of macrophages to TNF-α itself,[5 6] so that chronic elevation of serum TNF-α might lead to TNF-α production by tissue based macrophages. Pulmonary alveolar macrophages produce several times more TNF-α on stimulation than do circulating monocytes,[7] and we suggest that raised serum TNF-α concentrations in chronic inflammatory bowel disease could stimulate alveolar macrophages to produce more TNF-α, which would then act within the pulmonary microenvironment.

It is now clear that TNF-α can cause lung damage, and it is viewed as an important mediator in the adult respiratory distress syndrome (ARDS), which frequently supervenes in conditions such as septicaemia where serum TNF-α concentrations are grossly raised. Alveolar lavage fluid contains measurable TNF-α of pulmonary origin in ARDS.[8] Lesser elevation of serum TNF-α produces a more subtle derangement of pulmonary function, demonstrated well by the abnormal lung function tests found in patients treated for malignancy with recombinant TNF-α.[9]

We think that this mechanism would account for the activated alveolar macrophages found by Bonniere *et al*,[2] for the subtle lung function abnormalities found in many patients with active disease, for pulmonary granuloma formation, and for the more florid ARDS like picture found in many patients with life threatening toxic dilatation, where serum TNF-α may be much higher.[4]

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VIDEO REVIEWS

The Six Week Check of Infants. A video training package. Commissioned by: Nottingham Health Authority. Production Company: Chrysalis Television Midlands. Cost of training package (video and manual): £195; additional trainer's manuals £6 each. For details contact: Mrs B Whitchurch, Training Office, Nottingham Health Authority, Community Unit, Memorial House, Standard Hill, Nottingham NG1 6FX.

This package provides a very good basis for training sessions for general practitioners and other health care workers involved or becoming involved in child health surveillance. It should prove useful for both initial training and for update sessions for more experienced practitioners. The video consists of four parts (introduction, communication skills, the examination, and outcomes) plus as an 'activity' 18 slides of situations likely to be found during a surveillance check, where the participants are requested to write down the action they would take. There are two other activities based on sections of the video and very useful handouts, together with an evaluation form to complete the half day session. The package is designed to be highly interactive and to accommodate participants coming from varied levels of experience. It can be used flexibly with modifications to suit local needs.

The quality of the video varies from fair to excellent. Some of the slides used in the 18 situations section and elsewhere are of poor quality rendering interpretation difficult. There are some inconsistencies in the presentation, inevitable in such an unevaluated and rather controversial area of child health practice. The lack of agreement on terminology is discussed. In one section 'the doctor' who appears to be either a clinical medical officer or already a general practitioner doing surveillance is advised to sit down and discuss her findings with 'the health visitor' and with 'the GP' (a person who appears in another section of the tape as the link worker). Some may find the slightly patronising and proselytising approach of the presentation somewhat irritating especially the rather protracted section on the need for good communication.

Overall, however, the package is well thought out, well presented, and well worth buying for departments undertaking training in child health surveillance.

BRENT TAYLOR
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The School Entrant Review. A video training package. Commissioned by: Nottingham Health Authority. Production Company: Chrysalis Television Midlands. Cost of training package (video and manual): £195; additional trainer's manuals £6 each. For details contact: Mrs B Whitchurch, Training Office, Nottingham Health Authority, Community Unit, Memorial House, Standard Hill, Nottingham NG1 6FX.

However much paediatric experience the newcomer to community work may have, some time must be devoted to teaching the particular skills of the trade. This tends to follow the time hallowed industrial principle of 'sitting by Nellie' for a few sessions until deemed ready for useful work (not wishing to offend the one and only Nellie, listed on page 45 in current BPA handbook, by whom any aspirant community paediatrician would be well advised to sit; she cannot be expected to provide for the whole country). Properly organised classroom instruction in basic as distinct from the leading edge aspects of the craft remains rare. The ever innovative Nottingham department of community paediatrics has done us all a service in designing a course of instruction for both medical and nursing recruits to school health based around an instruction manual for the organisers, work sheets for participants, and a 45 minute, four part video. The course contains important lessons too for old stagers (your reviewer included) who could be subtly updated by exposure to this training package in the role of trainer. Selected parts of the package would be useful for teachers because it could help them to see what the school health service is all about and how they can work cooperatively with us. The same applies to school governors.

The trainer's manual tells one how to lay on the course, the equipment and type of venue needed, when to break for coffee, and the families one will need to recruit for demonstration purposes. The course starts with a historical overview of school health: where it came from, what it does now, and exposes the group to the current debates about its future, tending to side with preservation of the status quo, which should be taught to all paediatricians in training whatever their discipline. Carried out conscientiously, with first rate instructors, and good organisation, the manual on its own would form the basis of an excellent course. Video is a very powerful teaching tool; it is easy for armchair critics to carp and forget that it is exceedingly difficult to make well and expensive to accommodate second thoughts. I am glad that real professional staff and families were used instead of actors. I did not like all the messages and examples given, and although she was an excellent role model, would criticise the doctor's excessive use of leading questions. The manual goes into 'questioning techniques' in some detail and if used properly should correct this fault. I do not think that examining the upper abdomen of children who are standing up is good practice and it is a pity that testicular examination was not shown. The video, however, is only part of the course and local tutors are expected to expand on these points. The manual will be easier to modify in the light of experience as opposed to the video.

The school nurse in the video sat in the background and in real life I hope that she would have used her time more productively. The weighing scales used (£7·50 when I last visited Asda) take economy and inaccuracy to extremes. As long as points of this type are recognised and discussed no harm will result. What must not be done is to lend the video on its own to a new recruit to take home. It will be the intelligent use of the manual and the resulting group dynamic that will make or break this course; the video is a supplementary basis for discussion.

EUAN ROSS
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BOOK REVIEWS

Chronic Childhood Disease—An Introduction to Psychological Theory and Research. Christine Eiser. (Pp 174; £25·00 hardback, £8·95 paperback.) Cambridge University Press, 1990. ISBN 0-521-38519-9 (h/b), 0-521-38682-9 (p/b).

Every so often there is a piece of work bringing together research and thinking on a subject and acting as the source of reference for the next few years. In 1965 Vernon and colleagues published a comprehensive survey of literature on the effects of hospitalisation and illness in childhood.[1] Ten years later Pless and Pinkerton not only collected and sifted the literature on the psychology of chronic childhood disease, but began to provide a conceptual model of adjustment and maladjustment of the child with a chronic disorder in his family and society.[2] In the same year the psychologists Rachman and Phillips, in a brief but encouraging description of ways in which psychologists had already applied their skills to the problems of medical conditions and treatments, wrote one of the first tentative calls to clinical psychologists in Britain to turn their own attentions to the field of medicine.[3] Now Christine Eiser demonstrates how far the psychologists have come in the last 15 years in one area alone: the psychological effects of chronic disease on children and their families.

This book reviews and draws together the results of well conducted studies, and emphasises the relevance for clinical practice. Throughout, the emphasis is on children's illness and treatment experiences in the context of their development, and other aspects of their social lives. The book is kept to a reasonable length by largely excluding the major motor disabilities, blindness, deafness, and mental handicap.

The contents cover hospitalisation and pain management and the effects of chronic disease on educational achievement, self esteem, behaviour, and family life and other relationships. The developmental approach is exemplified in the discussion of the development of concepts about the body, illness, and death and the consequent importance of appropriate communication of information to sick children of differing ages to aid their realistic understanding and contribution to compliance with treatment regimes. Chapters on the encouragement of coping strategies, and important issues which may inform and determine future research, round off this comprehensive review.

This book stands a good chance of becoming the source book on the psychology of chronic childhood disease, at least until Christine Eiser needs to bring it up to date.

ROY HOWARTH
Consultant psychiatrist

1 Vernon DT, Foley JM, Sipowicz RR, Schulman JL. *The psychological responses of children to hospitalisation and illness: a review of the literature.* Springfield: Thomas, 1965.
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Pediatric and Adolescent Gynecology. 3rd Ed. By SJH Emans, DP Goldstein. (Pp 621; £35·00 paperback.) Churchill Livingstone (Little, Brown), 1990. ISBN 0-316-23399-4.

Confronted with ever increasing requests for advice on children and adolescents with genital signs and symptoms: I need this book.

A paediatrician and a gynaecologist have successfully collaborated to produce a sensible and sensitive guide to the common and important gynaecological problems of childhood and adolescence. It is written in a refreshingly non-dogmatic style with good references and suggestions for further reading. There are a number of helpful illustrations including some colour plates of normal and abnormal genital anatomy.

The first chapter describes the evaluation of the child with advice on how best to examine children and adolescents. This chapter does include techniques some would consider too invasive for 'routine' use. Particularly helpful are the details given on the variations in hymenal appearance. If we were all to use the terminology suggested here confusion would be avoided. I was happy to see my disbelief in the congenitally absent hymen supported with references. There are a total of 19 chapters with a number of appendixes. Two important early chapters consider 'ambiguous genitalia in the newborn' and 'vulvovaginal problems in the prepubertal child'. The latter chapter provides a commonsense approach to diagnosis and helpful suggestions on treatment. The attention paid to vulvovaginitis will be particularly welcome as this common troublesome symptom is frequently ignored or inadequately dealt with by traditional paediatric and gynaecological texts. The bulk of the remainder of the book focuses on puberty and adolescence (physiology as well as pathology) including a short but helpful chapter on the 'breast: examination and lesions'. Sexually transmitted diseases including human papillomavirus and HIV, contraception, and teenage pregnancy are all informatively discussed with up to date (1989) data and references.

Throughout the book care is taken to consider the psychosocial implications of the issues involved. Sexual abuse is kept in perspective. It is the topic of a separate chapter but pertinent reminders of its modes of presentation are found elsewhere.

Most of this book is of equal relevance to paediatricians and gynaecologists and one must agree with the authors that a dialogue is needed between the two specialities to ensure optimum care for children presenting with gynaecological symptoms. This book deserves to enjoy wide ownership throughout both paediatric and gynaecological worlds.

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Paediatric Formulary. 2nd Ed. Lewisham and North Southwark Health Authority, 1990. (Pp 163; £6 paperback.) Copies available from Mrs S Barnes, Pharmacy Department, Guy's Hospital, St Thomas Street, London SE1 9RT.

I was somewhat alarmed when this new edition of the *Paediatric Formulary* arrived in the post. In the three years since the first edition, the book has almost doubled in thickness. Can there really be so many new drugs that I have not heard about? How could the drug reps have let me down like this?

I was relieved to find that there were in fact only two dozen new drugs included, mostly cardiovascular or antimicrobial. The strength of this formulary has always been the notes accompanying drug dosages, with many now updated and more detailed, hence the increase in size. The tremendous clarity and ease of dosage calculation have been maintained.

The new sections at the back include an excellent one on paediatric immunisation and a useful list of proprietary names. The section on cardiopulmonary resuscitation is invaluable and I have found the dosage schedule easy to use in an emergency.

I have few criticisms. A magnifying glass is required to read the nomograms for calculating surface areas. The section on parenteral nutrition is not too useful as every hospital has its own regimen. The inclusion of a section on analgesia and sedation would have been very handy.

What about its main rival from Alder Hey which has just appeared as a new fifth edition? The book from Liverpool can still fit in a filofax and is also cheaper. Unfortunately due to its small size less information is given with no list of emergency drugs. My main worry, however, is the potential source of error in giving drug doses as total daily dose as all hospital drug charts require individual doses to be prescribed. I can claim neutrality but would always recommend the Guy's formulary.

Every paediatrician should carry this book and not rely completely on memory. Paediatric departments should make sure copies are freely available in the casualty department as well as on the ward for occasional paediatric prescribers. At £6 a copy it is a very cheap investment in these days of massive payouts by the courts.

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Infection in the Newborn. Edited by J de Louvois and D Harvey. (Pp 164; £39·50 hardback.) John Wiley and Sons Limited, 1990. ISBN 0-471-92679-5.

This book serves the important purpose of bringing together neonatal paediatricians and specialists in other areas who share an interest in perinatal infection. The coverage is wide ranging, from a stimulating first chapter on the cellular and biochemical pathology of the inflammatory response, and a chapter on postmortem findings, the chapters on specific types of infection (nosocomial infection, listeria, group B streptococci, viruses in general, HIV, septicaemia, and meningitis), sections on laboratory tests and treatment possibilities, and finally maternal infection.

In neonatology there is an inevitable preoccupation to treat at the earliest suspicion of infection. However, there are considerable unit to unit differences in details of practice in this difficult area. There is an attempt in this text to put local prejudices into a scientific and historical perspective. One specific problem is the accurate diagnosis of bacterial infection, and although laboratory diagnostic tests are not foolproof, it is suggested that combinations of them can be of use in rationalising the starting and stopping of antibiotics. Other contentious topics are aired including the choice between a combination of penicillin/aminoglycoside and a newer cephalosporin for early sepsis, and the place of routine lumbar puncture in 'infection screening'. The section on HIV, although it may age quickly, is a welcome review and practical guide. Going on to treatment, there is a detailed analysis of evidence for the efficacy of immunoglobulin therapy, and a mention of therapeutic manipulation colonising flora. However, the most exciting suggestion is that of 'inflammation modulating therapy', which could favourably alter the many secondary manifestations of infection.

There is some repetition of material on bacterial infection, and poor coverage of some topical issues in non-bacterial infection. For example, the chapter on viruses avoids subjects such as rubella, cytomegalovirus, and hepatitis B, and describes in some detail respiratory syncitial virus infection, which is not strictly a neonatal concern.

Overall, this collection of essays provides a useful update and source of references on infection for the clinician caring for the newborn.

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Choosing For Children: Parent's Consent to Surgery. By Priscilla Alderson. (Pp 251; £6·99 paperback, £17·50 hardback.) Oxford University Press, 1990. ISBN 019 286115 8 (p/b), 019 217774 5 (h/b).

Parents, and even their children, are well educated today about matters of health and disease. Consequently they expect much from modern medicine, usually nothing short of complete cure for their illness. If this is denied them they tend to feel that something has gone wrong and somebody is to blame. The seeds for litigation are sown. These are good reasons for giving the very best in medical communications. The best reason, however, for rendering optimal communications is that the patients deserve it and none more so than children and their parents. In short, optimal communication is what the major part of this book is about, especially that which is needed when what could be life or death decisions are required for determining the type of treatment given to a child with congenital heart disease. The author presents the problems of effectiveness and efficiency in parent counselling and the bioethics of decisions based upon her study of paediatric cardiology and cardiac surgery in the Hospital for Sick Children, Great Ormond Street, and the Brompton Hospital in London. Messages are of general application. The first part of the book provides conversations with parents and with doctors of all ranks. The subject is consent for treatment, be it surgical, investigational, or neither. The matters are awareness, willingness, and trust between doctors and families.

Good communication before consent is recognised increasingly in the adult world but is required in much greater depth and complexity where children are concerned and the agonising, wrestling with information in part or whole, guilt, and worry are of a greater order. Readers of the book are likely to change their practice as a result of learning much from parents who have partaken of the experience and comments of the author who has received them. A distinguished cardiac surgeon wrote as much in the foreword and recommended that all surgeons involved in the taking of consent should read the book. Physicians who do not have to obtain consent nevertheless could learn much about talking with parents and children.

The final pages are devoted to 'bioethics', which is compared with wandering in a jungle; but help is at hand. The difficulties in the subject are shown. It is worth reading to understand this aspect of doctors' practice. Subjects like deontology, duties, rights, utilities, respect for rational persons or autonomous persons, beneficence, morality, and clear reasoning are dealt with—hardly bedtime reading.

The author states that 'ethical medicine combines justice with care, principled decisions with the response to individual need'. Furthermore 'paediatrics leads the way in this kind of patient and family centred approach to medicine. It would be unfortunate if bioethics jeopardised this approach'. This is one good reason why children's doctors should know more about a subject upon which non-medical professional and lay people wax erudite.

I found that the recurring sandwich of comments, parents' and doctors' statements and anecdotes followed by comments to be somewhat tedious. Many of the parents' comments are to be expected. The matters dealt with are very important but the prolix style may deter busy clinicians from reading it unless the importance of the subject drives them to it. It is a brave introduction into a sphere that should become increasingly important in children's medicine.

O P GRAY

Neonatal Seizures. Edited by Claude G Wasterlain and Paul Vert. (Pp 318; $118 hardback.) Raven Press, 1990. ISBN 0-88167-641-1.

At some stage most paediatricians will have experienced a sinking feeling when faced with a neonate who is apparently having a fit. It is easy simply to prescribe phenobarbitone and perform a battery of (often useless) tests. However the questions whether the baby *is* actually having a fit, does the fit need treatment, why is it happening, what do I tell the parents, etc, are less simple. This book attempts to impart a logical view of the diagnosis and management of neonatal seizures. The book itself is the result of an international colloquium on neonatal seizures held in September 1987 and the list of contributors is impressive. The various authors have clearly been given the opportunity to bring their contributions up to date, an important fact in an area as constantly advancing as epilepsy. This is reflected in the references, which include several published in 1989.

The book is divided into five sections: clinical diagnosis, mechanisms of brain damage, cerebral blood flow and metabolism, ontogenesis of receptors and neurotransmitters, and pharmacology and therapeutics. The difficulty of diagnosis of neonatal seizures, particularly with respect to electroclinical correlation, is highlighted and consideration is given to aetiology, prognosis, and the pros and cons of treatment. Chapters are devoted to specific seizure syndromes including neonatal myoclonic encephalopathy and the benign neonatal seizures. The experimental sections are likely to prove heavy going for the non-neurologist and some prior knowledge would help in understanding the important human and animal work presented. However the effort devoted to reading these sections will be well rewarded. Although the extent to which these mechanisms apply to human seizures is unclear, some knowledge of the potential mechanisms of seizure generation, propagation, and neuronal damage allows a rational approach to the management of neonatal seizures. The final section deals with treatment. The efficacy of the commonly used antiepileptic drugs, difficulties of drug administration in neonates, and the potentially damaging effects of these drugs are discussed. The last chapter recognises the variations in diagnostic and therapeutic attitudes towards neonatal seizures and is devoted to a survey of medical practice in a small number of leading institutions—this may be useful to some of those actively involved in the management of neonatal seizures.

In the end the book raises as many questions as it answers. In attempting to summarise the discussion from an international meeting this book compresses a large amount of information into a relatively small space occasionally leaving the reader feeling somewhat 'shell shocked'. However it addresses an important and poorly understood area and will be of interest to neonatologists, paediatric neurologists, and indeed to those treating epilepsy in children of any age. I would recommend having it on your shelf.

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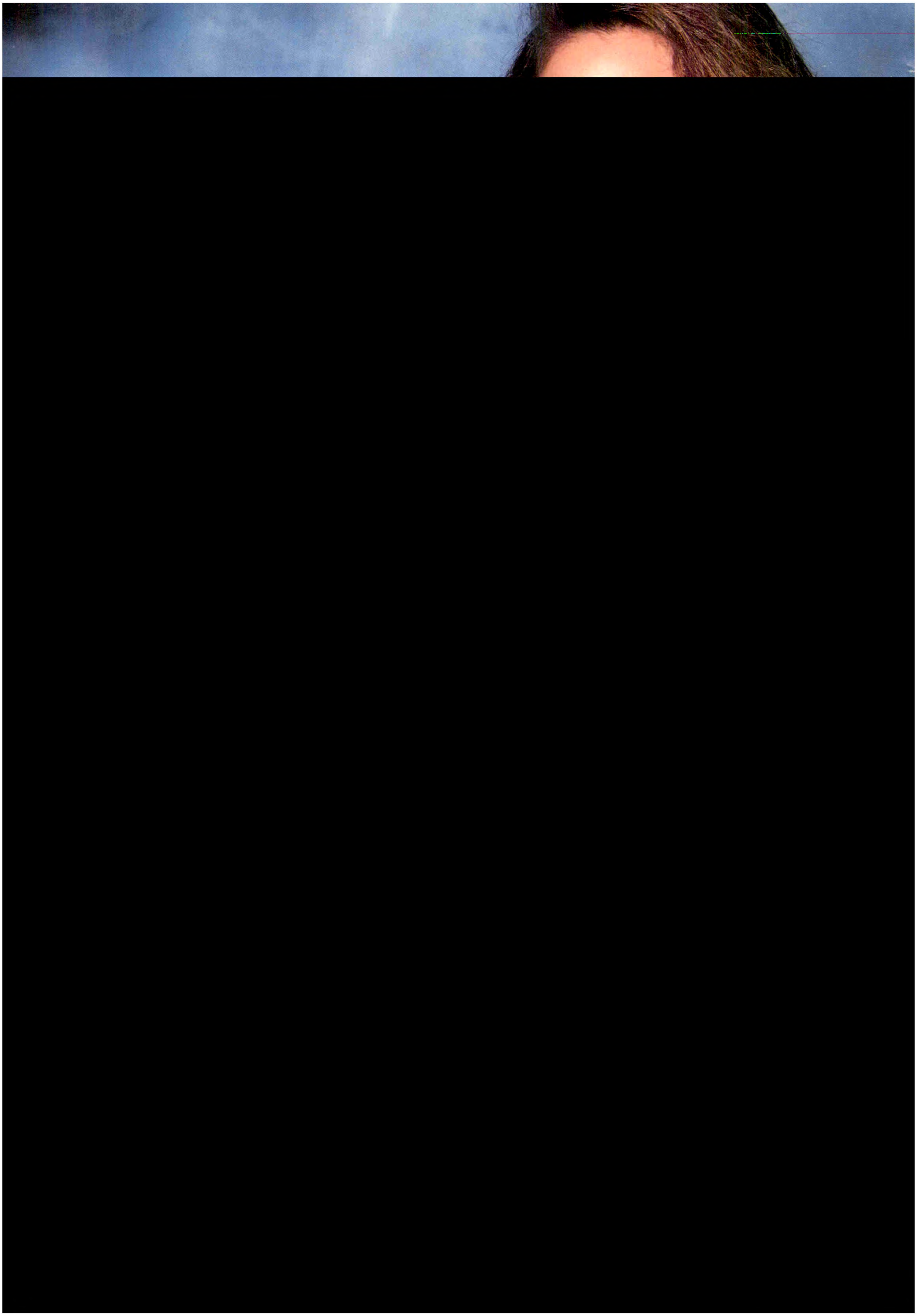
[redacted]



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FETAL AND NEONATAL EDITION

APRIL 1991 VOL 66 NO 4

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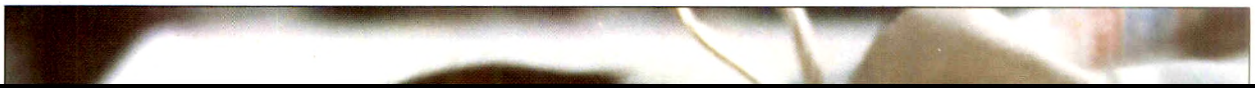
Some infants are ahead of their time.



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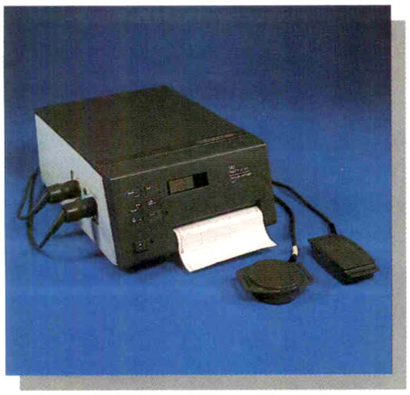

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Annotations

The use of plasma in the neonatal period

For many years the use of plasma and plasma expanders has been common in neonatal nurseries and they have taken a place in the armamentarium of therapies available to the neonatologist. There has been little scientific testing of their efficacy, however, despite this wide use in clinical practice at not inconsiderable cost.

The substances do have many admirable qualities: they contain protein, expand the circulating volume, and fresh frozen plasma contains clotting factors. As such these substances are attractive but on the other hand there are disadvantages—for example, they may produce circulatory overload and can transmit infection. It is therefore surpris-

[redacted]

profiles of sick newborn infants and set out to correct such defects with haematological success but with clinical failure.[2] This result was interesting but not surprising, as what was being done was to apply a fire extinguisher to a fire rather than to stop the fuel supply. Coagulation defects occur in the most gravely ill babies and are a consequence of rather than the cause of the clinical condition, improvement of which is of paramount importance.

POLYCYTHAEMIA

It was demonstrated by Stone *et al* that erythrocytes had a that treatment of the presenting life threatening event takes precedence over such disadvantages.

Albumin is also used before exchange transfusion to enhance bilirubin removal but the evidence for this is debated.[6] This means of treatment was employed extensively in the era of Rh haemolytic disease but is now much less often used.

RESPIRATORY DISTRESS SYNDROME

The facts that infants with respiratory distress syndrome are oedematous and have low serum albumin concentrations led to the idea that replacement may confer benefits. Greenough *et al* most recently expressed this possibility and showed that infusions caused a diuresis and weight loss in sick infants.[7] However, such studies really only support the contention that infants with respiratory distress syndrome are hypovolaemic and therefore suffer from underperfusion. What is unclear is whether this matters or not. Perhaps a more interesting line of study would be to look at the effects of plasma expansion early in postnatal life—there were studies in the late 1960s suggesting that umbilical cord oedema and serum albumin concentrations could be used as markers for the development of respiratory distress syndrome. What would happen now if we were to expand the circulating volume in the first few minutes of extrauterine life and then follow up with modern intensive care methods? It is unlikely that albumin will be curative but it might shorten or reduce the requirement for intensive care.

Conclusion

The use of these substances in neonatal care is widespread but poorly studied. This is unfortunate as any means of treatment must be formally assessed to ensure that it is properly used and maximum benefit obtained. Formal studies should be undertaken in order to achieve this goal.

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Is routine endotracheal suction justified?

New developments provide the opportunity to answer this and other questions quickly and inexpensively.

The precise role of routine endotracheal suction in intubated babies is controversial. Tracheobronchial suction can reduce respiratory system resistance[1] and should be performed whenever secretions accumulate, to prevent airway obstruction. However there are many potential hazards, including atelectasis,[2] bradycardia,[3 4] decreased lung compliance,[4] hypoxia,[4 5] transient increases in arterial and intracranial pressure and cerebral blood flow velocity,[4 6] bacteraemia,[7] and pneumothorax.[8–10] Although they are less noticeable, fluctuations in physiological variables due to suction still occur after paralysis[11] or when disconnection from the ventilator is avoided by using a side port adaptor.[12 13] Some of these hazards, for example pneumothorax, may be particularly dangerous in very preterm infants within the first three days of life,[14] a period when secretions are usually scanty. Because of the risks, some workers question whether routine endotracheal suction is justified.[4 6] Nevertheless, in many neonatal units endotracheal suction at intervals of one to six hours is still a routine procedure for all intubated babies, regardless of age or gestation. We remain collectively uncertain not only whether routine endotracheal suction is justified, but how it should be done. Sometimes the baby is 'preoxygenated', sometimes not. Usually suction is preceded by instillation of 0·25–0·5 ml normal saline but occasionally as much as 2·0 ml is used.[10] Sometimes the baby gets chest physiotherapy, which can increase the weight of secretions obtained[15] but may exacerbate hypoxia.

Endotracheal suction may be needed more often when inspired gas is poorly humidified, because this inhibits mucociliary clearance and thickens tracheobronchial secretions. In a non-randomised study, Lomholt *et al* reported a tenfold increase in the risk of plugging of the endotracheal tube with viscid secretions when inspired gas was less than 70% saturated at 37°C, which is equivalent to an absolute humidity of 31 mg H_2O/l.[16] It might thus be sensible to arrange for the hospital medical physics department to check periodically that intubated babies do not breathe gas of lower humidity than this, because inspired gas humidity varies widely during routine clinical practice (MFD O'Hagan *et al*, unpublished observations).

For the jobbing neonatologist, these issues raise important practical questions. Is it better to have a policy of suction only when impending airway obstruction is suspected than a policy of routine suction? If so—for which babies? Should endotracheal suction be preceded by chest physiotherapy?

These questions are most likely to be answered successfully in a large randomised controlled trial in which infants within each centre are randomly assigned to different policies. This would ensure that variations in case mix or clinical practice, which are inevitable, were balanced evenly between centres. To allow more than one question to be answered simultaneously a factorial design could be used so that infants were randomly assigned to either (a) routine endotracheal suction or (b) suction only when impending airway obstruction was suspected and, after the first 72 hours of life, to either (c) routine physiotherapy or (d) physiotherapy only when specifically indicated. Essential measures of outcome might include pneumothorax, duration of treatment with supplementary oxygen and with artificial ventilation, length of hospital stay, and abnormal ultrasound appearances at 6 weeks of age. It would be realistic to expect only a moderate reduction in the rate of any single adverse outcome, for example from 20% to 15%. A study would have a good chance (80% power) of showing such a reduction at a conventional level of significance (2p=0·05) if it recruited a total of 2000 infants.

Now that paediatricians, nurses, epidemiologists, and parents are collaborating on an unprecedented scale to investigate the role of surfactant in the OSIRIS and CURO-

SURF 4 trials*, studies of this size have become feasible. In both these surfactant trials, a common 'core database' of descriptive variables and essential outcome measures (including those just described) is routinely collected. If this large collaborative network continued, other important questions could be answered quickly and inexpensively. Perhaps the first step is to agree an agenda of questions to be addressed.[17] This might cover several other issues in respiratory management, such as the role of nasal or facemask continuous positive airway pressure before intubation in moderate respiratory disease,[18 19] or the optimum range of carbon dioxide or oxygen tension for mechanically ventilated preterm infants.[20] The advent of large scale cooperation among those who care for the newborn is a major development, and we should seize the opportunity to make it permanent.

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*Information about the OSIRIS trial can be obtained from Dr Adrian Grant, Director, Perinatal Trials Service, National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE and about the CUROSURF 4 trial from Dr Henry Halliday, Neonatal Unit, Royal Maternity Hospital, Grosvenor Road, Belfast BT12 6BB.

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ORIGINAL ARTICLES

Effects of hypoxaemia and bradycardia on neonatal cerebral haemodynamics

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Abstract

Near infrared spectroscopy has been used to assess the effects of bradycardia and hypoxia on the cerebral circulation in the premature neonate. The technique is well tolerated and can be applied in almost any infant. Continuous monitoring of changes in cerebral oxygenated, deoxygenated, and total haemoglobin is possible. Total haemoglobin is analogous to cerebral blood volume; thus information on circulatory changes as well as oxygenation state can be obtained. Twenty five babies had cerebral monitoring carried out using this technique. During episodes of hypoxia, both spontaneous and induced, impairment of haemoglobin oxygenation within the brain was detected together with an overall increase in the total mean haemoglobin concentration, which was $0{\cdot}8\times10^{-2}$ mmol/l. Bradycardia with apnoea also led to impairment of cerebral oxygenation, and to a rapid fall in the concentration of total mean haemoglobin to $1{\cdot}4\times10^{-2}$ mmol/l, which was followed in some cases by an increase to above the resting value on recovery of the heart rate to a mean of $0{\cdot}7\times10^{-2}$ mmol/l. These disturbances to total haemoglobin concentration represent abnormalities of cerebral blood volume that may be implicated in the pathogenesis of neonatal cerebral injury.

Neonatal cerebral injury is an important cause of morbidity and mortality in the low birthweight and premature infant, and occurs in a significant proportion of neonates despite advances in intensive care techniques.[1 2]

The aetiology of cerebral injury, both periventricular leukomalacia and periventricular haemorrhage, is not completely understood. Many risk factors have been identified as being associated with the development of cerebral injury,[3–5] but recent work suggests that the major underlying mechanism is disturbance to cerebral haemodynamics against the background of a developing brain with immature vasculature and impaired autoregulation.[6–8] Identification of such disturbance is extremely difficult in the neonate, and at best only single estimates of cerebral blood flow can be made by such methods as ^{133}xenon clearance and Doppler ultrasound.[9 10] A relatively new technique has been developed, near infrared spectroscopy (NIRS), which appears to have the potential to make continuous, non-invasive measurements of changes in oxygenated and deoxygenated haemoglobin and in total haemoglobin, which is related to blood volume in the tissue being studied.

Previous work by our group in perfused and in situ organs in animals has demonstrated that NIRS is an easily applied technique that can give rapid results in situations that may be changing very quickly.[11–13] We report here results which show that the technique can also be used to identify abnormalities of the cerebral circulation in infants. The aims of the study were to identify, using NIRS, any disturbances to cerebral blood volume and total haemoglobin and cerebral oxygenation that may occur in association with the commonly seen problems of hypoxia and bradycardia in premature infants.

Methods

NIRS

The technique of in vivo NIRS was first described by Jobsis,[14] and its potential value for use in the newborn was reported by Rea *et al.*[11] Brazy *et al* also described its application in the neonate.[15] Tissue is transilluminated by light in the near infrared region (700–1000 nm), which penetrates tissue much more readily than visible light. Certain chromophores within tissue show specific absorption characteristics, in particular oxygenated and deoxygenated haemoglobin.

Using several specific wavelengths in the near infrared part of the spectrum it is possible to monitor these chromophores within the brain.[11 16] The derivation of quantitative determinations is, however, less than straightforward. Algorithms that utilise the Beer-Lambert law and incorporate derived extinction coefficients for oxygenated and deoxygenated haemoglobin are used to convert changes in optical absorbance, A, to changes in concentration of the chromophores being studied. Near infrared multiplier coefficients for calculation of concentration changes for the three wavelengths used are given in the table.[17] For example the change in concentration of deoxygenated haemoglobin is given as: A1 $(1{\cdot}641)$–A2 $(0{\cdot}935)$–A3$(0{\cdot}178)$ where A1, A2, and A3 are the changes in absorbance at 775, 845, and 904 nm respectively.

Near infrared multiplier coefficients

Haemoglobin	*Wavelength (nm)*		
	775	*845*	*904*
Oxygenated	−1·156	0·074	1·428
Deoxygenated	1·641	−0·935	−0·178
Total	0·485	−0·861	1·249

INSTRUMENTATION

NIRS instrumentation has been developed by the department of biomedical engineering and medical physics, University of Keele. The instrument uses four laser diodes of wavelenghts 775, 805, 845, and 904 nm. The laser firing circuit is controlled by a microprocessor and provides light pulses of 200 ns duration that are transmitted along flexible glass optical fibres. Analysis of light transmitted through the biological organ is then carried out by computer using the near infrared multiplier coefficients as described above. Changes in concentration of oxygenated and deoxygenated haemoglobin and in total haemoglobin are displayed in real time.[11 12 18] The system achieves a coefficient of variation of 0·01% over a 30 second period while monitoring a basal level of eight optical density units. System drift is less than 0·004 optical density/hour for all four laser diodes.

The light energy produced falls well within safety limits as set by the British Standards Institute (BSI 4803). The near infrared system produces 0·133 Joules (J) per square metre (for single pulse) and 173 Watts (W) per square metre (mean power) compared with BSI limits of 200 J (single pulse) and 2000 W (mean power). A sensation of warmth occurs at 1000 W. No adverse effects of NIRS have been reported.

NEONATAL APPLICATION

For studies on the neonatal brain near infrared light at the appropriate wavelengths is transmitted along glass fibre optic bundles, through an attachment probe in which the light is turned through 90 degrees, thus enabling the fibres to rest alongside the baby's head. Double sided adhesive rings are used to keep the probes in place on opposite sides of the head on the temples. The interoptrode distance is measured with calipers between the surface of the two attachment devices. They are then bandaged in place. This is well tolerated by most infants, and other nursing and medical care can continue. The probes incorporate a safety switch that automatically stops the transmission of light if the probes become detached from the baby's head, in order to prevent the accidental entry of light into the eye.

QUANTITATIVE MEASUREMENTS

All values given are for changes in concentration from a baseline value during stable periods. In order to carry out absolute quantitation of results the determination of optical pathlength is required. As tissue is a complex, highly scattering medium, the optical pathlength is greater than the physical separation of transmitter and detector. Current estimates of optical pathlength give a value of approximately 4·5 times the interoptrode distance,[19] but it is generally accepted that further work is required in this area. Therefore no attempt is made here to measure absolute values because of the many assumptions required to do this and the remaining uncertainties regarding actual optical pathlength. In all plots shown the y axis represents change in concentration in mmol/l for the whole sample being studied. In order to make some comparisons between different babies (with different sized samples or heads), results are expressed per cm of sample size. This is derived from the physical interoptrode distance; the total change in concentration being divided by this figure to give change in concentration per cm of brain. The assumption is thus made that there is an association between optical pathlength and physical pathlength, which does not vary greatly with gestation.

Changes in the concentration of total haemoglobin are of great importance as they are considered to represent changes in blood volume of the sample being studied. In the brain all haemoglobin is contained within the vascular compartment unless haemorrhage has occurred. Provided that packed cell volume and therefore the association between plasma volume and haemoglobin remains constant, then changes in the concentration of total haemoglobin will reflect changes in total cerebral blood volume. For studies over a fairly short time period the packed cell volume can be assumed to be constant.

In order to express changes in haemoglobin oxygenation, the haemoglobin oxygenation index (oxygenated minus deoxygenated) is used. This enables comparison between babies and can be used in circumstances where there is a change in total haemoglobin.

Patients

(A) HYPOXIA STUDY

Sixteen infants with a total of 50 episodes of hypoxia were studied. These infants were all recovering from respiratory distress syndrome or had bronchopulmonary dysplasia and were still oxygen dependent at the time of study. Gestational age varied from 24 to 33 weeks (median 29), birth weight ranged from 580 to 2720 g (median 1012), and age at the time of study was from 3 to 105 days (median 20).

The babies were all stable in low concentrations of oxygen, and had normal cranial ultrasound scans or minimal abnormalities.

These babies were studied during spontaneous (n=20) or induced (n=30) falls in arterial saturation as measured by pulse oximetry (using an Ohmeda Biox 3700e). A change in arterial saturation of 5 to 10% was induced by altering the inspired oxygen for a period of five minutes, then returning this to the initial value. This change is considered safe, and is similar to that seen during nursing procedures and feeds. In those infants monitored during spontaneous fluctuations in arterial saturation the concentration of inspired oxygen was increased if the saturation fell below 80%.

In three babies also being monitored with transcutaneous carbon dioxide electrodes no significant change in skin carbon dioxide tension was seen, but it is possible that a transient brief rise in arterial carbon dioxide tension occurred. Continuous blood pressure data were not available for these studies as all indwelling lines had been removed by the time of study.

(B) BRADYCARDIA STUDY

In a second group of nine babies, a total of 15 studies were carried out during spontaneous bradycardias. In this group gestation varied from 24 to 30 weeks (median 27), birth weight from 580 to 1120 g (median 990), and age at the time of study from 3 to 96 days (median 20). The babies were either recovering from respiratory distress syndrome or had bronchopulmonary dysplasia, and they were all relatively stable in headbox oxygen. The bradycardias in all cases were considered to be related to apnoea of prematurity and not symptomatic of other illness—that is, infection, anaemia, etc, had been excluded. In some infants treatment with oral theophyllines had been started.

Monitoring was carried out during bradycardias with spontaneous recovery; if intervention was required then monitoring was terminated and the baby stimulated as appropriate.

As in the previous protocol, only three babies were of an age where transcutaneous carbon dioxide monitoring could be carried out. No change in skin carbon dioxide tension with bradycardia was detected, but again it is possible that arterial carbon dioxide tension changed in some infants. Direct blood pressure monitoring was not possible.

Approval from the local ethical committee was given for both studies and informed parental consent was obtained for each baby.

Results

Background noise while monitoring a baby in a stable state at rest was found to be ±0·0027 mmol/l for deoxygenated and ±0·0026 mmol/l for oxygenated and total haemoglobin.

(A) HYPOXIA STUDY

For babies studied during changes in arterial saturation, it was found that a fall in arterial oxygen saturation (SaO_2) was consistently associated with a change in oxygenation index as monitored by NIRS. The size of the fall was related to the degree of change in oxygenation index as can be seen in fig 1. In the majority of cases total haemoglobin (oxygenated plus deoxygenated), increased during arterial desaturation (mean $0{\cdot}8\times10^{-2}$ mmol/l of brain, SEM $0{\cdot}7\times^{10-3}$) (fig 2). No association was demonstrated between the change in total haemoglobin and the degree of desaturation. Figure 3 shows the results of a typical study on a baby of 30 weeks' gestation at age 5 weeks, during a period of induced desaturation. A rapid rise in deoxygenated and fall in oxygenated haemoglobin is seen as soon as the SaO_2 starts to fall, and both return to initial values as the saturation recovers. Total haemoglobin concentration shows a small increase with desaturation.

(B) BRADYCARDIA STUDY

The second group of babies were studied during bradycardic episodes accompanied by a fall in SaO_2. In all cases there was a fall in total haemoglobin immediately after the bradycardia (mean (SEM) 1·4 (0·16)$\times10^{-2}$ mmol/l of brain) (fig 2). Again in all cases as the bradycardia recovered to the original resting heart rate the total haemoglobin concentration increased up to the previous value. In nine cases total haemoglobin continued to increase to a concentration above the previous resting value after the bradycardia had recovered (mean (SEM) 0·7 (0·07)$\times10^{-2}$ mmol/l of brain) (fig 2).

Typical results from a baby studied during an episode of bradycardia are shown in fig 4. In this example total haemoglobin increased above the initial value after recovery of the bradycardia. The effects of multiple bradycardias in an infant of 28 weeks' gestation are shown in fig 5. The fluctuations in total haemoglobin and thus cerebral blood volume can be seen to follow closely the heart rate variation during these episodes.

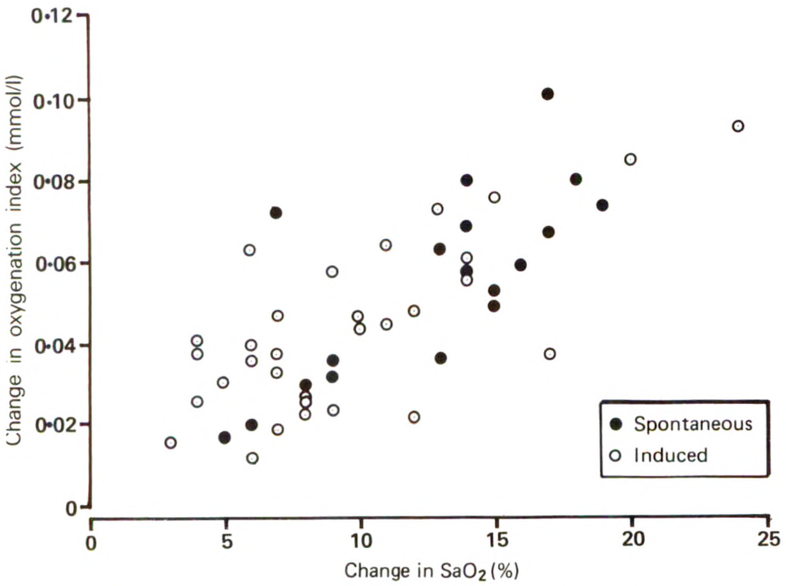

Figure 1 The association between change in SaO_2 and change in haemoglobin oxygenation index for 48 episodes of spontaneous and induced desaturation.

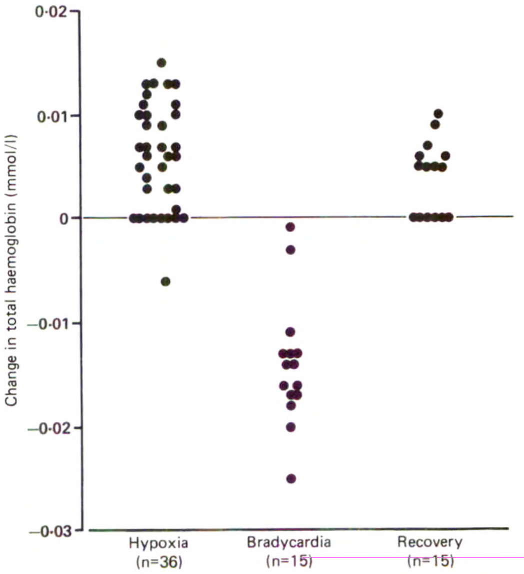

Figure 2 Changes in total cerebral haemoglobin in 36 episodes of hypoxia in 12 infants and 15 episodes of bradycardia with subsequent recovery in nine infants.

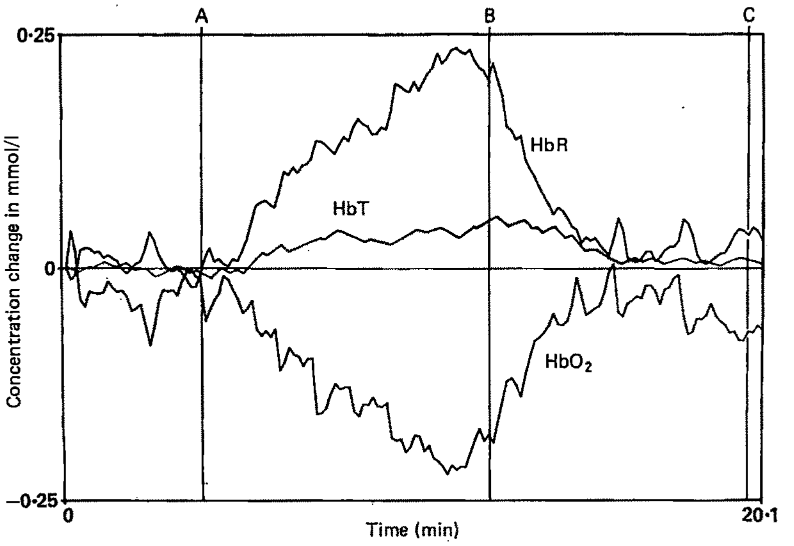

Figure 3 The effects of hypoxia on the concentrations of total (HbT), deoxygenated (HbR) and oxygenated haemoglobin (HbO_2) in a preterm infant of 30 weeks' gestation. Arterial saturation gradually falls from 94% at (A) to a lowest value of 83% at (B), then rises to 93% at (C).

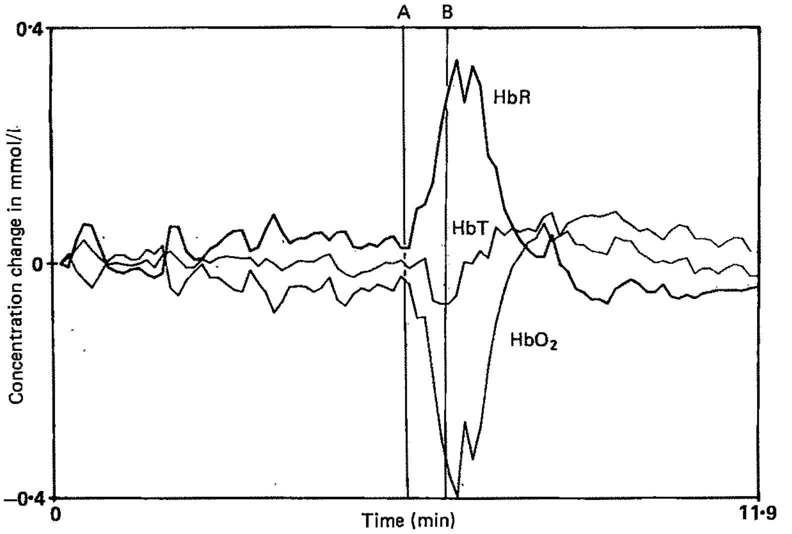

Figure 4 Changes in the concentrations of total (HbT), deoxygenated (HbR) and oxygenated haemoglobin (HbO_2) in a preterm infant of 27 weeks' gestation in response to bradycardia at (A). Heart rate fell from 144 bpm at (A) to 68 bpm at (B) with prompt recovery; arterial saturation fell from 91% at (A) to 60% at (B).

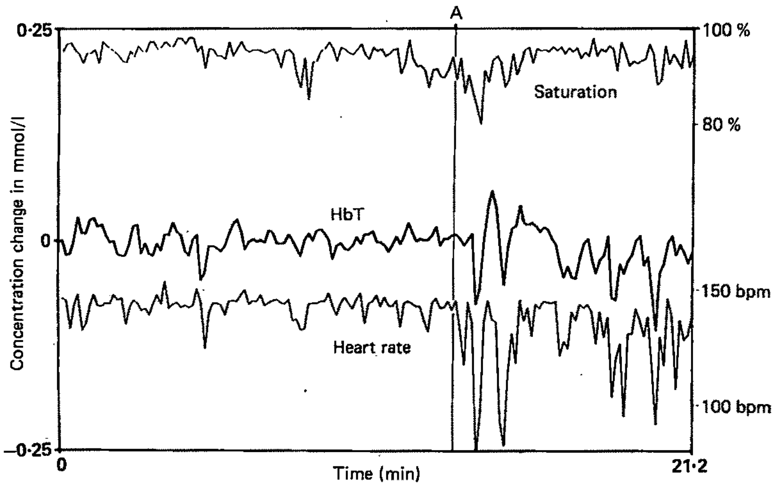

Figure 5 Changes in total haemoglobin (HbT), heart rate, and SaO_2 during multiple bradycardias beginning at (A), in an infant of 28 weeks' gestation.

Cumulative data on all the babies studied, indicating the change in total haemoglobin occurring either during bradycardia and recovery or during a saturation change, are shown in fig 2. These demonstrate that though the degree of change in total haemoglobin occurring during bradycardias was greatest, the order of magnitude for these changes was similar for all studies. In four cases the changes could not be analysed because of movement artefact.

Discussion

These studies have demonstrated that in most cases arterial desaturation of a moderate degree is associated with an increase in cerebral total haemoglobin, whereas bradycardia is associated with a fall in cerebral total haemoglobin, and in some instances with an overshoot on recovery.

Direct comparisons of results from babies of different gestation can raise some theoretical difficulties. The interoptrode distance for the babies studied was in the range 5·3 to 8 cm. Although the current estimate of optical pathlength is approximately 4·5 times the interoptrode distance, the use of this factor in babies of different gestational ages and weights, as well as the extent of variations in light scattering with differing stages of cerebral development, is yet to be fully evaluated.

Total haemoglobin concentration is related to cerebral blood volume under circumstances when haemoglobin and packed cell volume are remaining relatively constant, as in these studies over a fairly short time period. Thus changes in total haemoglobin during such studies represent changes in cerebral blood volume in association with specific clinical situations.

The most striking finding is of the fall in volume with bradycardia. In the neonate cardiac output is very dependent on heart rate, so a fall in heart rate would be expected to lead to a fall in cardiac output, cerebral blood flow, and thus cerebral blood volume.[20] Due to the technical difficulties discussed earlier in studying such parameters in babies, such expected changes have been difficult to demonstrate. Cooke *et al*, using jugular venous occlusion plethysmography, demonstrated a fall in estimated cerebral blood flow with fall in heart rate followed by an increase to above the resting level in two babies.[21] Some workers have suggested that as mean arterial blood pressure appeared to be maintained by a decrease in peripheral blood flow during apnoea and bradycardia, cerebral blood flow was likely to be maintained also.[22] In a study using Doppler techniques to measure cerebral blood flow velocity, however, both diastolic and systolic blood flow velocity decreased with bradycardia of less than 80 beats per minute.[23] The authors suggested that these changes, which paralleled similar changes in systemic blood pressure, would support the concept of a pressure passive cerebral circulation (that is, lack of autoregulation). These results are in accord with those found in our studies using NIRS. It would appear from these that cerebral blood volume is closely related to heart rate at least during single and multiple bradycardias.

Bradycardias and apnoeas in infants are usually treated vigorously but are very common in the premature baby. Although most respond rapidly to appropriate treatment, there are some babies who continue to have fairly frequent episodes. Such abnormalities of heart rate also occur during ventilation—for example, with suction, tube blockage, etc. Acute falls in cerebral blood volume, particularly if repeated, may well be one mechanism leading to ischaemia in areas at risk because of their immature blood supply. This could result in cerebral infarction—that is, periventricular leukomalacia.

In some babies an overshoot in total haemoglobin and cerebral blood volume is seen after a bradycardia. The reason for this is not clear. Although no significant change in transcutaneous carbon dioxide measurement was observed in those babies being monitored in this way, a rise in arterial carbon dioxide tension as a result of apnoea in association with the bradycardia could well lead to this phenomenon. It may also represent reactive vasodilatation due to hypoxia and acidosis induced by the bradycardia and apnoea.[24] Also of interest is the increase in total haemoglobin seen in some cases with desaturation. This may represent vasodilatation in response to even mild hypoxia. These results tend to suggest that the technique of using a small change in SaO_2 to calculate absolute cerebral blood volume, assuming that the latter does not change during the manoeuvre,[25] may be inaccurate.

CONCLUSIONS

Cerebral circulatory instability and abnormalities have been demonstrated in association with common neonatal problems and give further insight into the pathogenesis of ischaemic damage. NIRS has been shown to be capable of detecting such abnormalities non-invasively.

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Apnoea, bradycardia, and oxygen saturation in preterm infants

C J Upton, A D Milner, G M Stokes

Abstract

To analyse the effects of apnoea and bradycardia on the oxygen saturation (SaO_2) of preterm infants and to make recommendations for apnoea alarm limits, polygraphic recordings were made on 89 occasions of 27 preterm infants; 1029 apnoeic episodes were analysed. Reduction in SaO_2 was positively correlated with duration of apnoea, but the scatter of results was such that reductions in SaO_2 of up to 40% occurred with apnoeas of less than 10 seconds duration. The median initial SaO_2 was significantly lower in those episodes that resulted in bradycardia (92% compared with 95%), and there was also a significantly greater reduction in median SaO_2 (9% compared with 5%).

This study illustrates the difficulty of setting alarm limits for the detection of apnoea. We suggest that rather than simply detecting apnoea it is more appropriate to monitor heart rate and SaO_2 in infants with recurrent apnoea.

Apnoea of prematurity is one of the commonest problems encountered when caring for very low birthweight babies, and is likely to become more common as survival of such infants improves.[1] It is also associated with long term morbidity.[2] Despite this, we have little knowledge of the acute effects of apnoeic attacks on the oxygenation of small preterm infants. Previous studies have used transcutaneous oxygen monitors to measure these effects, but they have slow response times in comparison with the average duration of an apnoeic episode.[3–5] Pulse oximetry has been shown to be extremely accurate in a neonatal population and overcomes the problem of slow response.[6]

This study was therefore designed to examine the effects of apnoeic attacks on the oxygen saturation (SaO_2) of preterm infants, as measured by pulse oximetry, and see how this relationship is affected by the presence of bradycardia and treatment with methylxanthines. With this information we hoped to make recommendations for the setting of alarm limits for apnoea detection that would avoid hypoxaemia and so—we hoped—limit later morbidity.

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Subjects and methods

Babies born at 32 weeks' gestation or less were studied. The infants were clinically stable, breathing air at the time of study and were not preselected for the presence of apnoea. Eighty nine studies were performed on 27 infants, many of whom were studied longitudinally. Median birth weight of the infants was 1140 g (range 710–1700) and gestational age 29 weeks (range 25–32). Median day of study was 15 (range 1–55) and postconceptional age 32 weeks (range 26–36). There were 16 boys and 11 girls. Infants were receiving treatment with theophylline for apnoea during 45 of the 89 studies. A total recording time of 353 hours was analysed with a median study time of 3·96 hours (range 2·19–5·29).

SaO_2, an electrocardiogram, and two signals representing respiratory effort (thoracic impedance and abdominal respiratory inductive plethysmography) were recorded on to tape (Racal Store 4) throughout the study. SaO_2 was measured by an Ohmeda Biox 3700 pulse oximeter, which has been thoroughly evaluated for use in neonates.[6] The probe was sited over the dorsum of the foot and the standard six seconds averaging time for SaO_2 was used. This will have smoothed out some of the reductions in SaO_2 during short apnoeic attacks but was chosen to cut down on movement artefact, which is more common with a shorter averaging time. The electrocardiographic signal was recorded from a Life Trace 12 monitor using Arbo Pink electrodes, with one placed on each side of the chest and the reference lead on the back or abdomen. Agreement between oximeter wave form and electrocardiographic complex heart rates was checked regularly throughout each study. Thoracic impedance was recorded using an S and W Respiratory 8061 monitor and the electrocardiographic leads mentioned above. Abdominal respiratory inductive plethysmography was recorded from a locally constructed model (Respivest), with a single elasticated band placed at the level of the umbilicus. Two signals of respiratory effort are needed to record apnoeic episodes accurately,[7] and we have described our system in more detail elsewhere.[8] Recording was usually started after a feed, once the baby had settled to sleep and the signals had been verified on chart paper.

The polygraphic recordings were later viewed at X16 real time on a storage oscilloscope (Hitachi V-134) and any suspicious episodes played on to a Gould chart recorder at real time and then analysed manually. Apnoea was defined as cessation of breathing movement for at least 10 seconds, or a shorter period if associated with bradycardia of 90 beats/minute or less.

The effects of other variables on SaO_2 were analysed using simple and multiple regression. Changes in SaO_2 dependent on the presence or absence of bradycardia were analysed by the

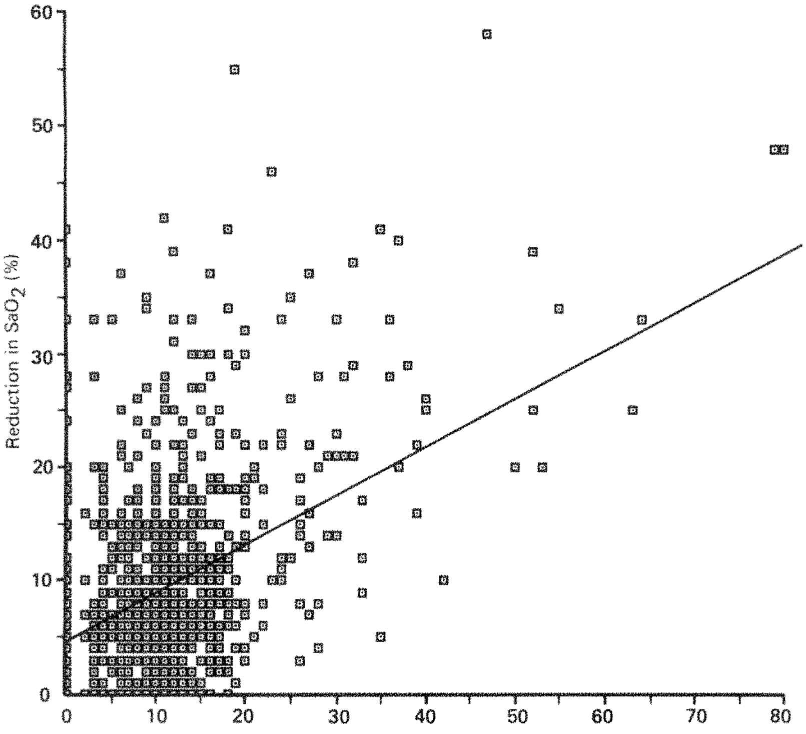
Mann-Whitney U test, and the effects of treatment with theophylline on bradycardia by the χ^2 test. Approval for the study was given by the Nottingham ethics committee and informed parental consent obtained.

Results

A total of 1029 episodes that fulfilled the above criteria were analysed. Of these, 605 were accompanied by bradycardia of which 83 seemed to occur without apnoea. Most of the bradycardias (522, 86% of the total) were therefore associated with apnoea. In 424 episodes apnoea occurred without bradycardia.

There was a positive correlation between the reduction in SaO_2 and the duration of apnoea ($r=0·41$, $p<0·0001$) (fig 1). From the regression line one might expect that for an episode of apnoea lasting 10 seconds the reduction in SaO_2 would be 9%, and for an episode lasting 20 seconds a reduction of 13% would be likely. This does, however, hide an enormous variation in the results, and reductions in SaO_2 of up to 40% occurred with episodes of apnoea lasting less than 10 seconds.

The initial SaO_2 value before the onset of an episode of apnoea also had an effect on the reduction in SaO_2, though it was weak ($r=0·18$, $p<0·0001$) (fig 2). Infants with poor baseline values of oxygenation, therefore, had greater reductions during apnoeic attacks than those who were well oxygenated. Such a relationship could have been predicted from the haemoglobin dissocation curve. Although the relationship was not strong, it remained significant in a stepwise multiple regression analysis when allowance was made for duration of apnoea, the presence of bradycardia, the frequency of apnoeic attacks, and treatment with theophylline. Of these other variables only treatment with theophylline did not have a significant effect on reduction in SaO_2.



BRADYCARDIA

[redacted]

Analysis of variables depending on whether infants were receiving theophylline at the time of study. Values are expressed as median (range)

	Infant receiving theophylline (45 studies, 535 episodes)	*Infants not receiving theophylline (44 studies 494 episodes)*
Initial SaO_2 (%)	92 (45–100)	94 (49–100)
Duration of apnoea (s)	10 (0–80)	11 (0–31)
Reduction in SaO_2 (%)	8 (0–58)	6 (0–55)
No of bradycardic beats	6 (1–73)	4 (1–36)
Lowest heart rate (beats/min)	74 (30–90)	77 (30–90)

SaO_2 between those episodes of apnoea of 10 to 14 seconds duration that were and were not associated with episodes of bradycardia ($p<0{\cdot}0001$, Mann-Whitney U test). Episodes not associated with bradycardia had a median 5% reduction in SaO_2 (interquartile range 3–8%, n=353), whereas those associated with bradycardia had a median reduction of 9% (interquartile range 5–14%, n=138).

TREATMENT WITH THEOPHYLLINE

Analysis of the effects of treatment with theophylline is confounded by the fact that those infants with the worst episodes of apnoea are treated. The differences between variables measured with and without treatment are shown in the table; there is only a small difference between the two groups. Apnoeic attacks that occurred during treatment with theophylline, however, tended to start with a lower SaO_2 value, to last longer, to have a greater reduction in SaO_2, and to produce a longer episode of bradycardia with a lower heart rate ($p<0{\cdot}0001$, Mann-Whitney U test). This clearly shows that treatment with theophylline was given to those infants with the most severe problems and does not show that such treatment had a deleterious effect. Theophylline did not, however, reduce the slope of the reduction in SaO_2 with respect to the duration of the apnoeic attack. In patients receiving theophylline the slope of the regression line was 0·41 ($r=0{\cdot}45$, $p<0{\cdot}0001$), and in those not receiving theophylline it was 0·40 ($r=0{\cdot}24$, $p<0{\cdot}0001$). The fact that the association between the reduction in SaO_2 and the duration of the apnoeic attack while receiving theophylline is closer than when not, has been noted previously.[9]

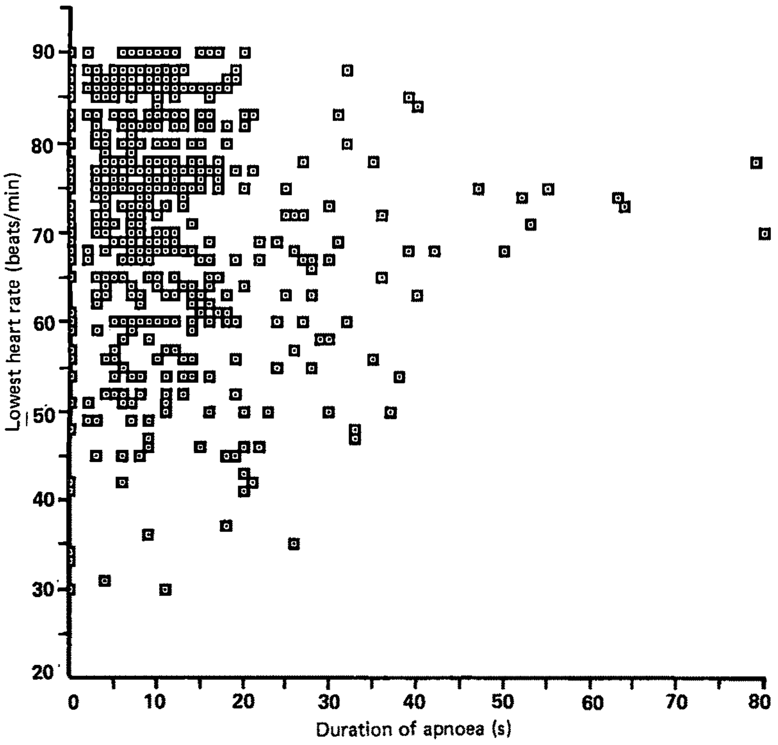


Figure 3 Minimal heart rate during episodes of bradycardia (beats/min) plotted against duration of apnoea (s). Minimal heart rate=74·22–0·14×duration of apnoea (r=0·11, p<0·0001).

Treatment with theophylline does not seem to protect against bradycardia either. There was a preponderance of episodes of bradycardia in the group treated with theophylline ($p<0{\cdot}001$, χ^2 test). This should not be interpreted as meaning that theophylline predisposes to bradycardia, but that the presence of bradycardia is important in the decision to start an infant on theophylline.

ALARM LIMITS

The absence of respiratory effort is not in itself likely to be deleterious to a preterm infant. Apnoea may be harmful if it produces a change in arterial blood gas tensions, most importantly hypoxaemia. Alternatively, damage may result from hypoperfusion caused by the ensuing bradycardia. Cerebral blood flow velocity in the anterior cerebral artery drops once heart rate falls to below 80 beats/minute.[10] Ideally, therefore, apnoea alarm limits should be set to prevent a fall in oxygen saturation and to keep the heart rate above 80 beats/minute. The fall in SaO_2 that would be acceptable is clearly an arbitrary decision. If one wanted to set an alarm limit to prevent a 10% drop in SaO_2, although the average episode of apnoea that causes this is of 12·5 seconds duration (fig 1), the spread is so great that no sensible alarm limit could totally prevent this degree of hypoxaemia. A much shorter alarm limit would, however, result in an unacceptably high number of alarms during apnoeic attacks not associated with falling SaO_2.

Similarly, it is difficult to extrapolate a sensible apnoea alarm limit from the degree of bradycardia that is produced. This is because the correlation between minimum heart rate during episodes of bradycardia and apnoea is extremely poor ($r=0{\cdot}11$, $p<0{\cdot}0001$) (fig 3). Bradycardia of less than 80 may occur with virtually any duration of apnoea, and therefore the minimum heart rate is not helpful in setting apnoea alarm limits. In practice this problem is overcome by routine electrocardiographic monitoring of infants at risk of apnoea.

Discussion

A poor degree of correlation between the duration of apnoea and the degree of oxygenation has been described by Peabody *et al* in a study in which they used transcutaneous oxygen monitoring.[3] There are other important factors that determine the fall in oxygen tension during episodes of apnoea, which they discussed; these include oxygen consumption, metabolic rate, and functional residual capacity. They blamed these other confounding variables for producing the poor correlation but, in addition, the slow response time of transcutaneous monitors must have added to the variability in their results. Indeed, Muttitt *et al* have more recently shown a closer correlation using pulse oximetry.[9] Their study, however, assumed that short episodes of apnoea were not harmful and only analysed those that lasted 15 seconds or longer. Our results have shown that this is a false assumption and that episodes lasting less than 10 seconds can result in reductions of SaO_2 of up to 40%. As a result of including shorter episodes of apnoea in our study, we have shown an even greater degree of correlation between reduction in SaO_2 and duration of apnoea.

Another important difference between our study and that of Muttitt *et al* is that they also monitored nasal airflow, whereas we only assessed external indicators of respiratory effort in detecting apnoea. This is important as in a clinical setting it is the apnoea alarms on these devices that we need to set, and relate to the oxygenation of the infant. Our study shows that the wide scatter of results makes this an almost impossible task, and that trying to relate duration of apnoea to heart rate is even more futile. Routine monitoring of nasal airflow is only done in a few neonatal units and it is interesting to note that when our study is compared with that of Muttitt *et al*, the use of airflow did not help to predict reductions in SaO_2 from duration of apnoea.

These data suggest that attempts to detect apnoea from external movements are not likely to be effective in preventing hypoxaemia in such infants. We would therefore suggest that a fundamental change is made in the way that we monitor infants at risk for apnoea. The poor correlation between heart rate and apnoea has meant that heart rate monitoring in apnoeic infants has become routine practice. Similarly we suggest that it is more appropriate to measure oxygen saturation in infants at risk to assess the degree of hypoxaemia being produced by the apnoea. The combination of electrocardiographic and SaO_2 monitoring would allow the detection of potentially damaging episodes no

that laryngeal chemoreflex bradycardia is potentiated in conditions of relative hypoxia.[12]

As episodes of apnoea that result in bradycardia start with a relatively low SaO_2, one would also expect a greater reduction in SaO_2 during an episode of bradycardia compared with an episode of apnoea not accompanied by bradycardia. We have shown this, but using a six seconds averaging time on our oximeter we were unable to study the temporal relationship between a fall in SaO_2 and the onset of bradycardia as described by Henderson-Smart *et al*.[13] They postulated that bradycardia was a peripheral chemoreflex response to falling SaO_2. We feel, however, that one should be wary of ascribing cause and effect to this relationship, as bradycardia is more common when there is an obstructive element to the apnoea,[14] and episodes of apnoea with such an element may also be associated with a more pronounced reduction in SaO_2.[15]

It seems, therefore, that a mild degree of hypoxaemia predisposes to both bradycardia and larger reductions in SaO_2. The implication of this is that it is important to keep infants with recurrent apnoeic attacks relatively well oxygenated. A delicate balance must be reached, however, to avoid hyperoxaemia, in view of the risks of development of retinopathy of prematurity. Unfortunately pulse oximeters are not reliable at excluding hyperoxaemia. The plateau at the top of the haemoglobin dissociation curve means that small increases in SaO_2 above 90% may be associated with large increases in arterial oxygen tension. Consequently an upper alarm limit of 95% on the pulse oximeter is unreliable at excluding hyperoxaemia.[16] It seems that 92% is a more realistic upper alarm limit for the Ohmeda Biox 3700 pulse oximeter.[6] Monitors vary considerably, however, and the optimal alarm limits[16] and accuracy[17] of different instruments also show wide variation. In addition, factors in the baby, in particular the amount of fetal haemoglobin, will affect the association between oxygen saturation and tension. We think therefore that in a baby with recurrent apnoea arterial blood gases should be checked to confirm hypoxaemia before the ambient oxygen

[redacted]

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Non-invasive assessment of pulmonary arterial pressure in healthy neonates

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Abstract

Doppler echocardiograms were carried out on 51 healthy babies three times during the first 72 hours of life to estimate pulmonary arterial systolic pressure by measuring regurgitant tricuspid jet velocity and applying the Bernoulli equation. Tricuspid regurgitation was detected at some stage in all preterm babies and most of those born at full term. Pulmonary arterial pressure could be measured from peak regurgitant velocity in babies with pansystolic regurgitation. The incidence of pansystolic regurgitation among 34 term babies at 0–12, 13–36, and 32–72 hours of age was 22, 27, and 19%, and in 17 preterm babies (within the same age groups) was 53, 50, and 31%, respectively. Estimates of pulmonary artery pressure in the term babies were in accord with known catheter values. Pressure fell rapidly during the first day in all 51 babies. The ratio of pulmonary:systemic arterial pressure was comparable between the two groups throughout. Ductal flow patterns mirrored the fall in this ratio with age—bidirectional flow was associated with a ratio of between 0·88:1 and 1·22:1 and high velocity left to right flow with a ratio of between 0·49:1 and 0·66:1. Both these techniques are non-invasive ways of assessing neonatal pulmonary arterial pressure.

Measurement of cardiac haemodynamics in neonates has always been difficult because it has required invasive techniques. There is, therefore, a paucity of good data particularly about the haemodynamics of the right heart.

By applying the modified Bernoulli equation to Doppler ultrasound measurements it is possible to estimate right heart systolic pressures non-invasively. The technique depends on tricuspid regurgitation being detected by Doppler echocardiography and has been validated extensively by simultaneous Doppler cardiac catheterisation studies both in adults and children.[1–5] In neonates, clinically detectable tricuspid regurgitation is present in persistent pulmonary hypertension of the newborn and after birth asphyxia.[6–8] It can present as a transient pansystolic murmur in healthy newborn infants.[9] Tricuspid regurgitation can be detected by Doppler in normal healthy subjects without clinical signs, allowing quantification of right heart systolic pressure in the normal population without resorting to invasive methods.[10–12] Tricuspid regurgitation detected by Doppler in the absence of clinical signs, however, may be less common in neonates than in older patients.[13] The objectives of this study were:

- To establish the prevalence of tricuspid regurgitation detected by Doppler ultrasound in healthy neonates during the first three days of life.
- To estimate systolic right heart pressures from tricuspid regurgitant jet velocity and the Bernoulli equation.
- To see how changes in ductal flow patterns correlated with estimated pulmonary arterial pressure.

Subjects and methods

Serial Doppler ultrasound examinations were carried out on 34 infants born at full term (birth weight 2615–4659 g) and 17 preterm infants (28–35 weeks' gestation, 1165–2290 g). Each child was examined within 12 hours of birth and daily thereafter for three days unless discharged sooner. All were born in good condition without perinatal asphyxia and none had respiratory distress requiring oxygen. The infants born at full term were recruited antenatally at parentcraft classes, and the preterm infants were enrolled as they arrived in the nursery (provided they were not oxygen dependent after 20 minutes). All but four babies in each group were born vaginally. Parental permission was obtained in all cases and ethical approval for the study was obtained from the district ethics committee.

At the first examination normal intracardiac anatomy was confirmed by cross sectional echocardiography and pulsed wave Doppler studies. Systolic upper limb blood pressure was measured by Doppler sphygmomanometry. Patency of the arterial duct was established using continuous wave Doppler ultrasound (2·2 MHz) by recording flow velocities from the pulmonary artery. Evidence of tricuspid regurgitation was sought, and where it was found the maximal velocities were recorded.

TRICUSPID REGURGITATION AND THE BERNOULLI EQUATION

The Bernoulli equation is a measure of fluid mechanics and relates the pressure drop between two chambers to the velocity of the fluid passing between them.[14] The peak velocity of blood is measured using continuous wave Doppler ultrasound which, unlike pulsed wave Doppler, can measure high velocities. The velocity is converted into a pressure drop by application of the modified Bernoulli equation: $P=4V^2$, where P is the pressure drop (mm Hg) and V is the velocity of blood (metres/second).

The technique was first used clinically to assess mitral or aortic stenosis[15–17] and may also be used to measure the drop in pressure across ventricular septal defects.[18]

In the right heart the drop in pressure from the right ventricle to the right atrium in systole can be assessed by applying the Bernoulli equation: right ventricular pressure−right atrial pressure=4×(tricuspid regurgitation jet velocity)^2.

Systolic pulmonary arterial pressure is equal to right ventricular systolic pressure if there is no pulmonary stenosis. Hence systolic pulmonary arterial pressure is equal to the drop in pressure in systole between the right ventricle and the right atrium plus the right atrial pressure. In neonates shortly after birth right atrial pressure is close to zero[19–21]; in calculating pulmonary arterial systolic pressure in healthy babies in this paper we have assumed it was zero. Application of the Bernoulli equation to the tricuspid regurgitant jet velocity should therefore estimate systolic pulmonary arterial pressure.

Measurement of the maximal tricuspid regurgitant jet velocity is simple. A blind continuous wave probe (2·2 MHz) was directed towards the tricuspid valve and a Doppler wave form was obtained (fig 1), and babies with any evidence of tricuspid regurgitation were recorded as having 'detectable tricuspid regurgitation'. In a subgroup of these babies the systolic regurgitant jet was detectable throughout the whole of systole and the maximal velocity was easily seen. These were recorded as having 'measurable tricuspid regurgitation', and systolic pulmonary arterial pressure was calculated for these babies. To measure maximal jet velocity accurately the Doppler probe must be in line with the direction of flow. To achieve this a range of apical, subcostal, and lower left sternal edge approaches were tried. The highest velocity recorded was interpreted as being in line with the jet; these values were usually obtained at the lower left sternal edge.

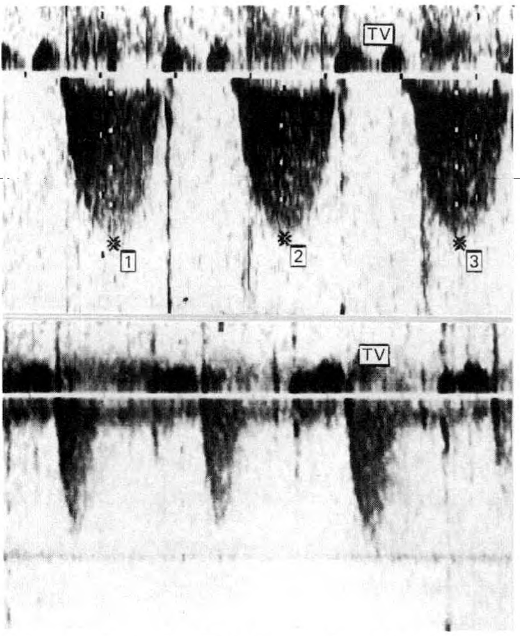

Figure 1 Examples of Doppler waveforms. Upper: measurable tricuspid regurgitation. The Doppler signal continues throughout the whole of systole and the maximal velocity can easily be seen (numbered 1, 2, and 3). Lower: tricuspid regurgitation detected but not measurable. The signal appears in early systole but is then lost, and the peak velocity cannot be seen. TV, tricuspid valve.

EVALUATION OF DUCTAL FLOW

Ductal flow was assessed by continuous and pulsed wave Doppler. A blind (2·2 MHz) continuous wave probe was placed at the upper left sternal edge and directed posteriorly towards the pulmonary artery. The velocities and flow pattern were recorded. The pulmonary artery and duct were visualised on cross sectional echocardiography, and with a duplex scanner the pulsed wave sample was placed at the pulmonary end of the arterial duct. Care was taken to ensure an angle of incidence of less than 20° to the direction of the arterial duct.

Results

INCIDENCE OF TRICUSPID REGURGITATION

The incidence of tricuspid regurgitation is shown in table 1. Doppler studies were positive in most babies in both groups and at some stage in all preterm babies. Detectable tricuspid regurgitation was more common among the preterm group at all ages and significantly in babies aged 37–72 hours. Measurable tricuspid regurgitation was significantly more common in the preterm group in the first 12 hours than in the term group, the proportion falling significantly with time. Neonates who had measurable tricuspid regurgitation on the third examination were re-examined 24 hours later, but measurable tricuspid regurgitation was found in only two term babies who were still under 72 hours of age. The preterm babies were all re-examined after 72 hours and none had measurable tricuspid regurgitation.

DERIVED SYSTOLIC PULMONARY ARTERIAL PRESSURES

Calculated pressures for the term and preterm groups are plotted in figure 2A and B. The values in the preterm babies are lower than those in the term babies, but they show a similar pattern of change against time. Furthermore,

Table 1 Incidence of detectable and measurable tricuspid regurgitation in preterm and term neonates divided into three age groups

	Term infants			*Preterm infants*		
	0–12 h (n=32)	*13–36 h (n=30)*	*37–72 h (n=27)*	*0–12 h (n=15)*	*13–36 h (n=16)*	*37–72 h (n=16)*
Mean age (hours)	5	25	50	6	27	44
No (%) in whom tricuspid regurgitation detected	23 (72)	18 (60)	15 (56)**	14 (93)	14 (88)	15 (94)**
No (%) in whom tricuspid regurgitation measurable	7 (22)*	8 (27)	5 (19)	8 (53)*	8 (50)	5 (31)

*p<0·05 **p<0·02, Fisher's exact test.

when pulmonary arterial pressure is expressed as a ratio of systemic blood pressure (fig 3) the results from the two groups are almost identical. Differences in the pulmonary: systemic arterial pressure ratios between the preterm and term groups were assessed by relating group and age to the logarithm of the ratio using multiple linear regression. There was no significant difference between the groups (p>0·8). The change with time is partly related to the fall in pulmonary arterial pressure, but it is also related to an increase in systemic blood pressure, which is most obvious in the preterm group. The systemic blood pressure measurements are shown in table 2.

COMPARISON WITH NEONATAL CARDIAC CATHETERISATION DATA

The best available data on pulmonary arterial pressures in neonates were obtained in 1964 by Emmanouilides *et al* who catheterised 51 healthy unsedated term babies.[22] Our data show similar absolute values and similar changes with time (fig 2A). Statistical comparison was made by the same method as we used to compare the term and preterm groups—that is, the logarithm of pulmonary arterial pressure was related to group and age using multiple linear regression. Some babies in our study had serial measurements, but the study of Emmanouilides *et al* was entirely cross sectional. To permit valid statistical comparison between these two different types of data, one value was selected at random from each of the five babies in our study who had multiple values. The data exhibit considerable variability and this is only partially explained by the regression model. There were no significant differences between the groups overall (p>0·5) or the way in which the pressure fell with time (p>0·8).

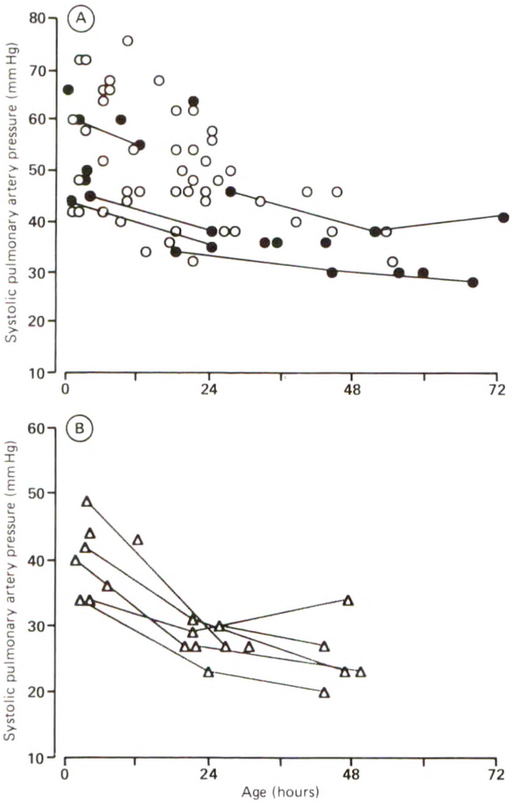

Figure 2 Derived systolic pulmonary artery pressure in 15 healthy neonates: (A) (22 measurements) values in neonates in this study born at full term (●) compared with 49 values in 51 babies (four were identical) measured by cardiac catheterisation by Emmanouilides et al (○)[22]; and (B) 11 preterm neonates (21 measurements) (△). Sequential examinations in the same baby are joined by lines.

Table 2 Mean (SD) systolic upper limb blood pressure (mm Hg) in term and preterm neonates divided into three age groups

	0–12 h	*13–36 h*	*37–72 h*
Preterm	49·4 (9·3)** (n=17)	56·3 (6·4)** (n=17)	58·8 (9·3) (n=17)
Term	60·6 (6·3) (n=34)	63·0 (8·0)* (n=31)	71·6 (6·0)* (n=28)

* and **=p<0·005, paired *t* test.

DUCTAL FLOW

We studied the pattern of ductal flow using continuous and pulsed wave Doppler as described. The flow pattern obtained was compared with the ratio of pulmonary:systemic arterial pressures in those babies with both measurable tricuspid regurgitation and a patent duct. Eleven babies with measurable tricuspid regurgitation had bidirectional flow (forward in systole, backwards in diastole). The ratio of pulmonary to systemic arterial pressure in these babies was between 0·88:1 and 1·22:1. High velocity left to right flow with maximal velocity in late systole was seen in seven babies with measurable tricuspid regurgitation and their arterial pressure ratios ranged from 0·49:1 to 0·66:1. An intermediate type of flow was seen in five babies with continuous low velocity left to right flow, (lowest in systole and higher in diastole); in these the ratios ranged from 0·74:1 to 0·92:1. One baby with a ratio of 0·79:1 had a ductal wave form that varied with respiration from bidirectional to intermediate.

In summary, when derived pulmonary arterial pressure approached systemic pressure, the flow in the pulmonary artery was bidirectional, and conversely low pulmonary arterial pressures were associated with continuous retrograde high velocity flow indicating that calculated pressures do genuinely reflect pulmonary arterial pressure.

Not all babies with bidirectional flow in the pulmonary artery (indicating high pulmonary arterial pressure) had tricuspid regurgitation that was measurable on Doppler. In the term group there were 19 babies with bidirectional flow in the first 12 hours. Only seven of these (37%) had measurable tricuspid regurgitation. In the preterm group five of the seven with bidirectional flow (71%) had measurable tricuspid regurgitation, suggesting that preterm infants are more likely to have physiological tricuspid regurgitation than term infants if they also have pulmonary hypertension.

The proportion of babies with patent ducts at each examination and the ductal flow patterns seen are shown in table 3. In the first 12 hours 19 of the 30 term babies (63%) and seven of the 16 preterm babies (44%) with patent ducts had

Table 3 Ductal patency and flow velocity patterns among term and preterm neonates divided into three age groups

	Term infants			*Preterm infants*		
	0–12 h (n=34)	*13–36 h (n=31)*	*37–72 h (n=28)*	*0–12 h (n=17)*	*13–36 h (n=17)*	*37–72 h (n=17)*
Flow velocity:						
No (%) bidirectional	19 (56)	1 (3)	0	7 (41)	0	0
No (%) intermediate left to right	6 (18)	3 (10)	0	5 (29)	2 (12)	0
No (%) high velocity left to right	5 (15)	11 (35)	4 (14)	4 (24)	6 (35)	3 (18)
No (%) with patent duct	30 (88)	15 (48)	4 (14)	16 (94)	8 (47)	3 (18)

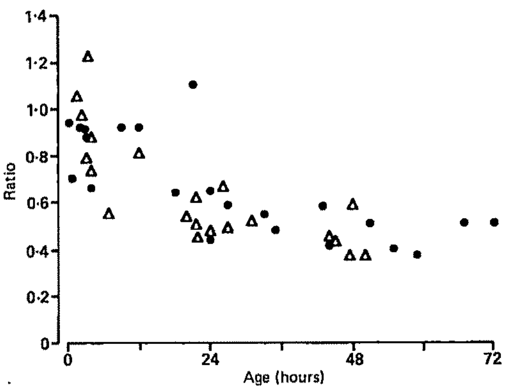

Figure 3 Systolic pulmonary artery pressure expressed as a ratio of systemic blood pressure in 11 preterm neonates (21 values) (△) and 15 neonates born at term (22 values) (●).

bidirectional flow. The fact that nine of 16 preterm babies (56%) had pure left to right flow during the first 12 hours of life suggests that the pulmonary to systemic arterial pressure ratio falls faster in preterm babies during this time. After 13 hours of age pure left to right flow predominates in both groups and bidirectional flow was seen in only one term baby. At 21 hours, this was the only baby to present with a transient soft systolic heart murmur consistent with tricuspid regurgitation. The data point representing a relatively high pulmonary arterial pressure (pulmonary to systemic arterial pressure ratio 1·1:1) can be seen as an outlier in figure 3.

Discussion

In this study most healthy neonates had Doppler evidence of tricuspid regurgitation without clinical signs, and in an appreciable proportion it was possible to measure the maximal velocity. Systolic pulmonary arterial pressure could be estimated from the right ventricle to right atrial pressure drop (assuming that right atrial pressure approximated to zero). Pulmonary arterial pressure fell quickly in both the premature and the term babies, and the pulmonary to systemic arterial pressure ratio was similar in the two groups. This pattern of change with time was also mirrored by ductal flow patterns. Our finding that the pattern of ductal flow changed as the ratio of pulmonary:systemic arterial pressure changed is consistent with results of studies comparing data on ductal flow velocities with results of simultaneous cardiac catheterisation.[23 24]

Our observation that pulmonary arterial pressure falls as quickly in the preterm as in the term baby is in conflict with the findings from a recent study by Evans and Archer.[25] These authors used a different Doppler technique to monitor circulatory changes in the newborn,[26] which quantifies changes in the shape of the velocity wave form at the pulmonary valve by pulsed wave Doppler. The time to peak velocity (acceleration time) is divided by the total ejection time and this ratio is inversely related to pulmonary arterial pressure. This method may be less suitable for neonates because the positioning of the pulsed Doppler sample at the pulmonary valve is critical,[27] and the ratio is affected by heart rate and myocardial function,[28] and the presence of tricuspid regurgitation.[29] Cooper *et al* found that this method was not reliable in children with ventricular septal defects if they also had pulmonary hypertension,[30] and Chan *et al*, comparing three different Doppler methods of assessing pulmonary hypertension in adults and children, concluded that measurement of tricuspid regurgitant jet velocity was the technique of choice.[31]

Though the method used in this study has the advantage that it should not be affected either by heart rate or by myocardial performance, a major disadvantage is that we were only able to estimate pulmonary arterial pressure in babies with measurable tricuspid regurgitation. It is possible that babies without tricuspid regurgitation have different pressures; our evidence, however, does not support this. Our results were consistent with previous catheter studies, and ductal flow patterns showed a similar fall of pressure with time in babies with and without tricuspid regurgitation. Furthermore, if the presence of measurable tricuspid regurgitation was dependent merely on pulmonary hypertension then we would not have been able to make sequential measurements in babies as the pulmonary arterial pressure fell. Factors other than pulmonary artery pressure are obviously affecting the competence of the tricuspid valve.

We have shown that two different Doppler techniques for estimating pulmonary arterial pressure have correlated well and that the calculated pressures were consistent with data from neonatal cardiac catheterisation. The only thing that was not done was to compare direct and indirect measurement in the same baby at the same time. Clearly this is no longer an ethical option in healthy neonates. The technique has been extensively validated at other ages and we can see no reason why the age of the subject should alter the validity of the technique. Nevertheless, this method is the subject of a continuing validating study using data from cardiac catheterisation in infants without right heart disease that will also define limits of variance and error in the technique.

We have found Doppler evidence of tricuspid regurgitation at some stage in most healthy babies during the first three days of life. The detection of tricuspid regurgitation by Doppler cannot therefore be interpreted in isolation as a sign of cardiopulmonary distress at this age. Measurement of the maximal tricuspid regurgitant jet velocity seems to be a useful way of measuring systolic pulmonary arterial pressure non-invasively in a high proportion of babies shortly after birth. The values presented in this paper show how systolic pulmonary arterial pressure changes in relation to systemic pressure over the first 72 hours. The technique may be of practical value in the management of cardiopulmonary distress, as tricuspid regurgitation is a common finding in babies with the respiratory distress syndrome.[32] The method we have described, combined with analysis of ductal flow patterns, seems to be a promising addition to techniques of neonatal intensive care.

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Postnatal changes in cardiac output and haemorrheology in normal neonates born at full term

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Abstract

Circulatory adaptation was studied serially in 11 healthy term neonates on days 1, 3, and 5 by cross sectional and pulsed Doppler echocardiography. Changes in the determinants of blood viscosity (packed cell volume, plasma viscosity, red cell aggregation, and red cell deformability) were studied on day 1 and day 5. There was a 27% increase in the cardiac output as a result of increasing stroke volume, whereas heart rate did not change significantly. Mean blood pressure increased by nearly the same extent as cardiac output (21%), so that the overall resistance remained unchanged. Packed cell volume, red cell aggregation, and red cell deformability did not change significantly during the first five postnatal days. Plasma viscosity rose significantly (by 12%) so that whole blood viscosity increased during that period. As there was no change in overall systemic vascular resistance the vascular hindrance—calculated as the ratio of resistance: blood viscosity—decreased, thereby indicating vasodilation.

Blood flow in circular vessels is determined by Poiseuille's law with the Hagenbach extension. This means that blood flow (Q) increases with increasing pressure gradient (that is, pressure drop divided by vessel length, $\sigma P/L$) and increasing vessel radius (r), and decreases with increasing blood viscosity (η):

$$Q=\frac{\pi}{8}\times\frac{\sigma P}{L}\times\frac{r^4}{\eta}$$

By applying this simplified model to the entire vascular system, it can be calculated that cardiac output increases as arterial blood pressure and generalised vasodilation increase, and decreases as blood viscosity increases. This model may also be used to calculate the resistance to blood flow (R) as a ratio of arterial blood pressure and cardiac output:

$$R=\frac{P}{Q}=\frac{8}{\pi}\times\frac{L}{r^4}\times\eta$$

L/r^4 expresses the effect of the vessel geometry on the flow resistance ('vascular hindrance', Z). This term was introduced by Lamport[1]; η represents the effect of blood properties on flow resistance:

$$R=\frac{P}{Q}=Z\times\eta$$

As P, Q and η can be measured, Z can be estimated from these variables:

$$Z=\frac{P}{Q\times\eta}=\frac{R}{\eta}$$

In healthy full term neonates, systolic blood pressure increases by an average of 2 mm Hg/day during the first five days after birth.[2] Serial studies of cardiac output during the first postnatal days, however, have given conflicting results. Mahoney *et al* found a decrease in peak Doppler flow velocity in the aorta during the first three days after birth.[3] Alverson *et al* and Arcilla *et al* found little change in cardiac output during the first five postnatal days, although their studies were not designed to examine this defined time period.[4 5] In lambs, cardiac output/kg body weight decreases from birth to 4 weeks of age.[6 7] The decrease between week one and week two seems to be the result of an appreciable increase in body weight. The decrease in cardiac output was also associated with an appreciable fall in oxygen consumption. In piglets cardiac output was found to rise with age.[8] In foals cardiac index increases considerably during the first two weeks as a result of increasing stroke volume and decreasing vascular resistance.[9]

The present study was designed to measure cardiac output, arterial blood pressure, and determinants of blood viscosity in healthy full term neonates during the first five postnatal days.

Subjects and methods

NEONATES

A total of 11 healthy neonates of gestational ages ranging from 38 to 41 weeks (median 40) and birth weights ranging from 2700 to 4350 g (median 3300) were studied after permission had been obtained from the human subject research committee of the University Hospital Centre of Heidelberg. All the infants were delivered vaginally after uneventful pregnancies. Cords were clamped 10 to 20 seconds after birth. Informed consent was obtained from the parents in each case.

CARDIOVASCULAR VARIABLES

Cardiac output and blood pressure were measured on the first day of life (at between 2 and 11 hours) and on days 3 and 5. During the examination, which was made at least an hour after the last feed, infants were either sleeping or quiet. None of the infants had received drugs or intravenous fluids. Infants were examined lying supine under radiant heaters to maintain a core temperature of 37°C.

Cardiac output was measured using pulsed Doppler ultrasound as previously described.[10] The flow velocity integral of the maximal velocity in the ascending aorta was measured from the apical position.

The cross sectional aortic area was calculated from the M mode echocardiogram by the leading edge to leading edge method using a standard parasternal approach. Cardiac output was calculated from the equation cardiac ouput= cross sectional aortic area (cm^2) multiplied by flow velocity integral (cm) multiplied by heart rate/minute. Length of the evaluated heart beats was measured by computer, so heart rate could be calculated. Examination time for cardiac output measurements averaged 10 minutes. All measurements were done by one investigator (VM). Intraobserver variability for cardiac output determination was 14%.

Blood pressure was measured by a Doppler device (Arteriosonde, Kontron–Roche). Mean blood pressure was calculated as: mean systolic blood pressure plus twice the mean diastolic blood pressure divided by three. Flow resistance was calculated as pressure:flow ratio. Vascular hindrance was calculated as the ratio of flow resistance:blood viscosity.

BLOOD SAMPLES

Two blood samples were studied from all 11 neonates. Placental blood (5 ml) was taken from the umbilical cord immediately after cord clamping and before delivery of the placenta. The second blood sample (2 ml) was collected by venepuncture on day five. The blood was anticoagulated with 1 mg/ml EDTA. The second blood sample was also used for the routine screening tests.

GENERAL HAEMATOLOGICAL VARIABLES

Packed cell volume was measured in duplicate by the microhaematocrit method. The values were not corrected for trapped plasma, which is about 2% in full term neonates and adults.[11] Red blood cell count and haemoglobin concentrations were measured with a cell counter (Contraves). Total plasma protein concentration was measured by the biuret test. Plasma fibrinogen, IgM, and α_2-macroglobulin concentrations were measured by a radioimmunodiffusion technique (M-Partigen kits, Behring).

HAEMORRHEOLOGICAL VARIABLES

All haemorrheological measurements were made at 22°C within four hours of blood collection. Plasma viscosity was measured with a tube plasma viscometer (Plasmaviskosimeter KSPV4, Myrenne). Blood viscosity in 100 μm tubes was calculated as the product of the measured plasma viscosity and the relative viscosity. Relative viscosity was derived from a previously published relative blood viscosity/haematocrit relationship for full term neonates.[11] Red cell aggregation was assessed using the Myrenne Erythrocyte Aggregometer MA2, which consists of a transparent cone plate viscometer.[12] A blood sample with an adjusted packed cell volume of 0·40 is sheared for 20 seconds to disperse all red cell aggregates. The drive motor is then stopped, and the light transmission increases with the time at a rate proportional to the rate of red cell aggregation (that is, at a rate proportional to the formation of cell free liquid gaps between aggregates). The increase in light transmission during a 20 second period is measured and displayed as an aggregation index.

The deformability of single red blood cells was observed and measured using a counter-rotating, cone plate rheoscope (Effenberger, Munich),[13] which was mounted on an inverted microscope (Leitz Diavert).[14] Five shear stresses from 7 to 112 dyn/cm^2 were applied, and the length and width of 40 red blood cells were measured in each sample at each shear stress. Red blood cell deformation was calculated as length minus width divided by length plus width. For the red cell deformability measurements, blood was diluted 1:50 (packed cell volume about 1%) in phosphate buffered saline containing 350 g/l of dextran 70 (Pharmacia), which has a mean (SD), osmolality of 295 (5) mmol/kg and a viscosity of 35 mPa/second at 25°C.

STATISTICAL ANALYSES

The cardiovascular and haemorrheological variables studied on days 1 and 5 were compared with the Wilcoxon rank sum test for paired observations; a probability of less than 0·05 was accepted as significant. Regression analysis was used to make overall correlations among independent variables measured on days 1 and 5.

Results

The cardiovascular variables are shown in table 1. Cardiac index, stroke volume, and blood pressure increased by 27%, 13%, and 21%, respectively, during the first five days after birth. Vascular resistance did not change. The haemorrheological variables are shown in table 2. Plasma viscosity, and total plasma protein and plasma fibrinogen concentrations increased significantly during the first five days by 12%, 11%, and 32%, respectively. The increase in red

Table 1 Mean (SEM) changes in cardiovascular variables during the first five postnatal days

	Day 1	*Day 3*	*Day 5*
Cardiac output (ml/min/kg)	151 (10)	180 (12)	192 (12)*
Stroke volume (ml)	4·6 (0·39)	4·6 (0·43)	5·2 (0·46)*
Heart rate/min	120 (3)	127 (4)	124 (3)
Mean blood pressure (mm Hg)	39 (1·1)	44 (3·4)	47 (4·7)*
Resistance (mean blood pressure divided by cardiac output)	258 (17)	244 (25)	244 (12)
Vascular hindrance (resistance:blood viscosity)	86 (5·6)	Not measured	72 (3·5)*

*p<0·05 compared with day 1.

Table 2 Mean (SEM) changes in determinants of blood viscosity from day 1 to day 5

	Day 1	*Day 5*	*p Value*
Packed cell volume	0·49 (0·1)	0·52 (0·1)	>0·05
Total plasma protein (g/l)	55 (6)	61 (8)	<0·05
Fibrinogen (g/l)	2·13 (0·3)	2·81 (0·7)	<0·02
IgM (g/l)	0·34 (0·04)	0·4 (0·05)	<0·05
α_2-Macroglobulin (g/l)	5·47 (1·5)	5·10 (0·79)	>0·05
Plasma viscosity (mPa/s)	1·10 (0·02)	1·23 (0·03)	<0·05
Erythrocyte deformability shear stress:			
7 dyn/cm^2	0·35 (0·03)	0·35 (0·02)	>0·05
28 dyn/cm^2	0·48 (0·04)	0·49 (0·02)	>0·05
112 dyn/cm^2	0·57 (0·03)	0·58 (0·004)	>0·05
Erythrocyte aggregation	4·02 (1·6)	4·93 (1·9)	>0·05
Calculated blood viscosity (mPa/s)	3·00 (0·30)	3·39 (0·69)	<0·05

cell aggregation was not significant ($p<0{\cdot}10$). Calculated whole blood viscosity increased between days 1 and 5 by 13% ($p<{\cdot}05$). Vascular hindrance (calculated as the ratio of vascular resistance:blood viscosity) therefore decreased within the first five postnatal days by 16% ($p<0{\cdot}05$). A decrease in vascular hindrance indicates vasodilation.

For correlation analysis the results of days 1 and 5 were combined. There were significant linear correlations between plasma fibrinogen concentration and plasma viscosity ($r=0{\cdot}58$; $p<0{\cdot}001$) and between plasma fibrinogen concentration and erythrocyte aggregation ($r=0{\cdot}41$; $p<0{\cdot}05$).

Discussion

In the present study cardiac output increased significantly during the first five postnatal days as a result of an increase in stroke volume. This increase in cardiac output (27% between days 1 and 5) was nearly twice as high as the intraobserver variability for this method reported by others[15] and our group.[10]

Moreover, the increase in cardiac output was associated with an increase in blood pressure and indications of vasodilation. Only a few studies have been reported on the postnatal changes in cardiac output, and these have been done at different times. Mahoney *et al*[3] and Wilson *et al*[16] measured aortic blood flow velocity with Doppler ultrasound and found an insignificant decrease in flow of 10% from day 1 to day 3. Alverson *et al* studied aortic blood flow velocity for the first time within the first four days after birth, then weekly until the age of 6 weeks, and every other month during the first year of life.[4] They observed a nearly constant aortic blood flow velocity during the first year of life. As the aortic cross sectional area increased proportionally to body weight, cardiac output/kg varied little during the first year. During the first week of their study cardiac index increased by 8%. Cord clamping times are not given in these reports.

Arcilla *et al* compared pulmonary and systemic blood flow changes (dye dilution) in neonates who had early or late cord clamping.[5] On the first day neonates whose cords had been clamped late had a higher left ventricular output as a result of the higher blood volume, compared with those whose cords had been clamped early. Both groups had a decrease in systemic flow resistance of about 10% during the first 24 hours after birth. In the group whose cords had been clamped late, the left ventricular output/m^2 increased by about 4% between days 1 and 2. In the present study cords were clamped 10 to 20 seconds after birth so that the infants probably received a placental transfusion of 10 to 20 ml/kg.[17]

Several papers have reported a steady increase in arterial blood pressure with increasing age and weight.[2] We found similar increases in cardiac output and blood pressure during the first five postnatal days. Thus, the flow resistance (computed as ratio of blood pressure: cardiac output) remained unchanged. Flow resistance is often used as an indicator of vessel geometry, but in circular vessels it is the product of blood viscosity and vascular hindrance. Blood viscosity in vessels or tubes with rapid flow (for example, the aorta) increases as the plasma viscosity and packed cell volume increase and the red cell deformability decreases. Packed cell volume and red cell deformability remained unchanged during the first five days. As blood viscosity rises linearly with increasing plasma viscosity, blood viscosity probably increased by a percentage similar to plasma viscosity (table 2). Because the flow resistance remained constant during the first five days, vascular hindrance (computed as the ratio of blood flow resistance:blood viscosity) decreased by a similar extent as the blood viscosity rose (table 1). In other words, the increasing blood viscosity was compensated for by viscodilatation.

The rise in plasma viscosity during the first five postnatal days was related to the increase in plasma protein concentration. Plasma viscosity depends on the total plasma protein concentration but is more influenced by high molecular weight proteins like fibrinogen than by small proteins like albumin. Red cell aggregation is also principally caused by fibrinogen, which forms bridges between adjacent erythrocytes.[12] The slight but not significant postnatal increase in red cell aggregation can also be explained by the increase in plasma fibrinogen concentration. Under physiological conditions erythrocyte aggregation takes place only in veins, where shear stresses are low. Strong red cell aggregation may impair venous return. Red cell aggregation in neonates is low compared with healthy adults.[12] The 20% increase in red cell aggregation during the first five postnatal days probably did not affect cardiac output.

We conclude that in healthy, full term neonates cardiac output increases during the first five postnatal days, and this increase is associated with increasing arterial pressure and vasodilation. The potential negative effect of blood viscosity on cardiac output seems to be compensated for by vasodilation.

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Atrial natriuretic peptide and blood volume during red cell transfusion in preterm infants

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Abstract

Because raised plasma concentrations of atrial natriuretic peptide indicate volume expansion, we studied the effect of red cell transfusion on plasma atrial natriuretic peptide concentration, packed cell volume, and intravascular volume in eight preterm infants. Red cell transfusion increased red cell mass, packed cell volume and erythrocyte count, but decreased plasma volume. Total blood volume, plasma atrial natriuretic peptide concentration, urine flow rate, and urinary sodium excretion did not change.

We conclude that a slow transfusion of less than 10 ml red cells/kg body weight does not cause volume expansion with subsequent atrial natriuretic peptide release thereby affecting the cardiovascular system.

Preterm infants weighing less then 1500 g are often given red cell transfusions to replace blood losses and to treat refractory anaemia.[1] Because haemoglobin concentration and packed cell volume correlate poorly with the red cell mass/kg of body weight in preterm infants,[2 3] it has been proposed that the red cell mass rather than the packed cell volume should be used for estimation of the red cell deficit.[4]

The volume expansion resulting from red cell transfusion increases the risk of intraventricular haemorrhage in preterm infants.[5 6] Atrial natriuretic peptide is released when volume expands in children[7] as well as in fetuses.[8] Raised plasma concentrations of atrial natriuretic peptide have been found in preterm infants with respiratory distress syndrome,[9] increased sodium intake,[10] and with patent ductus arteriosus.[11 12] Moreover, atrial natriuretic peptide concentrations seemed to correlate with volume changes in preterm and full term neonates.[9 13 14] This indicates that atrial natriuretic peptide may be a sensitive indicator of volume changes. There have been to our knowledge no studies on the effect of transfusion on plasma atrial natriuretic peptide in preterm infants. We have therefore studied the packed cell volume, intravascular volume, and plasma concentration of atrial natriuretic peptide in preterm infants before and after transfusion of red blood cells.

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Patients and methods

Eight preterm infants with a median gestational age of 28 weeks (range 25–34) and birth weight of 1025 g (range 650–1800) received red cell transfusions for anaemia at a median of 41 days of age (range 1 to 96). Their median weight was 1710 g (range 650–2660). All infants were in good clinical condition. Four were mechanically ventilated through an intratracheal tube. None had renal disease, shock, sepsis or were being treated with diuretics. The volume of transfused red cells was calculated to raise the packed cell volume to 0·45 (haemoglobin to 155 g/l). The transfusion rate averaged 0·05 (0·01) ml/min/kg.

Before and one hour after red cell transfusion blood was drawn in EDTA coated tubes (1·5–2 ml) for determination of plasma atrial natriuretic peptide and haemoglobin concentrations packed cell volume, haemoglobin F concentration, and plasma osmolality. In addition 0·5 ml blood was drawn in plastic tubes for measurement of serum sodium, potassium and creatinine concentrations. The packed cell volumes of all red cell concentrates were also measured.

Timed urine specimens were collected before, during, and after red cell transfusion for measurement of the urinary flow rate, creatinine, osmolality, and sodium and potassium concentrations.

The circulatory red cell mass of the infants was estimated from the dilution of haemoglobin F by the transfused red cells (that is, by haemoglobin A) as described by Phillips *et al.*[4] Haemoglobin F was estimated by a modified alkali denaturation procedure.[15] Red cell mass (RCM) before transfusion was calculated from the transfused red cell volume (V), and the haemoglobin F percentages before (HbF 1) and after (HbF 2) the transfusion.[4]

$$\text{RCM}=\frac{\text{V}\times\text{HbF 2}}{\text{HbF 1}-\text{HbF 2}}$$

Red cell mass after transfusion was calculated as the sum of the pretransfusion red cell mass and transfused red cell volume. Total blood volume was calculated from the red cell mass divided by the packed cell volume. Plasma volume was derived by subtraction of the red cell mass from the total blood volume. In adults whole blood packed cell volume is usually calculated by multiplication of the venous packed cell volume by 0·9; as in preterm infants the whole body:venous packed cell volume ratio may vary widely we have not corrected the venous packed cell volume.[16] Plasma atrial natriuretic peptide was measured by radioimmunoassay after extraction as previously described.[7]

Statistical analysis was done by the Wilcoxon rank sum test for paired observations and correlations were calculated by the method of least squares. Values are given as mean (SEM). The study was approved by the ethics committee of the University Children's Hospital and

Table 1 Laboratory findings before and after red cell transfusion in eight preterm infants. Figures are expressed as mean (SEM)

	Before red cell transfusion	*After red cell transfusion*	*p Value*
Body weight (g)	1070 (200)	1060 (200)	
Packed cell volume	0·35 (0·21)	0·43 (0·26)	<0·02
Haemoglobin (g/l)	120 (7)	136 (8)	<0·02
Erythrocyte count ($\times 10^{12}$/l)	3·4 (0·2)	4·5 (0·2)	<0·02
Red cell mass (ml/kg body weight)	32·3 (6·4)	39·0 (6·2)	<0·02
Total blood volume (ml/kg body weight)	91·9 (14·2)	90·8 (11·5)	<0·78
Plasma volume (ml/kg body weight)	59·0 (8·2)	51·8 (5·8)	<0·02
Serum sodium (mmol/l)	140·2 (0·8)	140·5 (1·9)	<0·49
Serum chloride (mmol/l)	102·6 (2·4)	104·0 (2·4)	<0·25
Serum potassium (mmol/l)	5·1 (0·2)	4·9 (0·4)	<0·29
Plasma osmolality (mmol/kg)	284·0 (11·9)	283·7 (7·0)	<0·68
Plasma atrial natriuretic peptide (pmol/l)	50·1 (16·2)	48·0 (17·8)	<0·72

Table 2 Clearances, urine flow rate, and absolute and fractional excretion of sodium and potassium before, during, and after red cell transfusion in preterm infants. Figures are expressed as mean (SEM)

Urine flow rate (μl/min/kg):	
Before	37·1 (8·3)
During	45·8 (7·6)
After	50·0 (12·5)
Creatinine clearance (μl/min/kg):	
Before	840 (220)
During	860 (170)
After	830 (190)
Osmolar clearance (μl/min/kg):	
Before	28·5 (9·0)
During	32·3 (6·4)
After	35·5 (9·8)
Free water clearance (μl/min/kg):	
Before	8·6 (5·7)
During	13·6 (7·3)
After	9·5 (7·9)
Urinary excretion of sodium (μmol/min/kg):	
Before	2·0 (0·8)
During	2·6 (0·6)
After	3·0 (1·0)
Fractional excretion of sodium (%):	
Before	2·5 (1·0)
During	3·6 (1·8)
After	3·6 (1·6)
Urinary excretion of potassium (μmol/min/kg):	
Before	0·6 (0·2)
During	0·7 (0·2)
After	0·7 (0·2)
Fractional excretion of potassium (%):	
Before	17·5 (3·4)
During	20·7 (4·8)
After	19·8 (4·8)

None of the differences are significant.

informed consent was obtained from the parents in each case.

Results

Red cell transfusion resulted in a significant increase in red cell mass, packed cell volume, haemoglobin, and erythrocyte count ($p<0{\cdot}02$ in each case, table 1). Plasma volume fell ($p<0{\cdot}02$). Total blood volume, plasma concentration of atrial natriuretic peptide, serum concentrations of sodium and potassium, and plasma osmolality did not change (table 1). Transfusion did not significantly alter urine flow rate, creatinine clearance, osmolar and free water clearances, and absolute and fractional excretions of sodium and potassium (table 2). There was no significant correlation between red cell mass and packed cell volume, haemoglobin, or red cell count.

Discussion

The results indicate that slow transfusion of red cells (0·05 (0·01) ml/min/kg) increases the amount of circulating erythrocytes in preterm infants without significantly affecting the cardiovascular system by acute volume load and subsequent atrial natriuretic peptide release. As the average intravascular volume did not rise, the average plasma atrial natriuretic peptide concentration also remained unchanged (table 1). Consequently, urine flow rate, creatinine clearance, and sodium excretion did not change significantly, although five of eight infants showed slight increases in urinary flow rate, urinary sodium excretion, and fractional sodium excretion. These measurements fell in the three other infants, however, indicating that in this small group of patients there was no consistent response of natriuresis and diuresis after red cell transfusions.

The exact mechanism of atrial natriuretic peptide secretion is not fully understood. Distension of the left and the right atrium is associated with atrial natriuretic peptide release.[17 18] It is not known what degree of volume expansion is necessary for atrial distension gross enough to result in subsequent atrial natriuretic peptide release. In studies on the association of acute volume expansion and rise in plasma atrial natriuretic peptide, blood volume was expanded by 30%.[17 19] We have recently shown that rapid volume loading with whole blood during exchange transfusion in newborns is associated with an increase in plasma atrial natriuretic peptide concentration.[20] Our present study suggests that if the volume expansion is slow enough or small enough it does not cause the atrial stretch that results in subsequent atrial natriuretic peptide release.

Pretransfusion red cell mass was not significantly related to packed cell volume, haemoglobin concentration, or erythrocyte count. This confirms the results of Phillips *et al*,[4] who found a weak correlation between red cell mass and packed cell volume in 33 preterm infants ($r=0{\cdot}32$). This can be explained by a variation of total blood volume in preterm infants.

Although we calculated transfusion volume to raise the haemoglobin concentrations to 155 g/l we reached only a mean haemoglobin concentration of 136 g/l. In our experience this is common in clinical practice. Perhaps the formula on which such calculations are based (3 ml of packed red blood cells×kg body weight×haemoglobin deficit in g/100 ml) should be revised.[21]

We conclude that a slow transfusion of less than 10 ml of red cells/kg body weight does not affect the cardiovascular system by volume expansion leading to subsequent release of atrial natriuretic peptide.

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Fatal persistent pulmonary hypertension presenting late in the neonatal period

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Abstract

Two cases of fatal idiopathic persistent pulmonary hypertension presented late in the neonatal period. Lungs were examined histologically by light and electron microscopy, and immunocytochemical studies were used to identify nerves. There was extension of medial smooth muscle distally along the arterial pathway so that most precapillary arteries had completely muscular walls, which in some cases completely obliterated the vessel lumen. Enlarged endothelial cells also contributed to the reduction in the size of the lumen. Nerve fibres accompanying muscular arteries were found in the alveolar region, more distal than is normal. The predominant neuropeptide was the vasoconstrictor tyrosine.

Possible aetiological factors in persistent pulmonary hypertension of the newborn are increased muscularity of the peripheral pulmonary arteries antenatally, an increase in the number of vasoconstrictor nerves, or an imbalance in the production of leukotrienes and prostacyclins in the perinatal period.

Persistent pulmonary hypertension of the newborn is a failure of the pulmonary circulation to adapt successfully to postnatal life. Associated with a wide variety of neonatal cardiopulmonary disorders, it is characterised by an inappropriately high pulmonary vascular resistance with subsequent right to left shunting of blood at the foramen ovale, the ductus arteriosus, the lungs, or a combination. In this paper we describe two fatal cases of idiopathic persistent pulmonary hypertension of the newborn in infants who presented late in the neonatal period. The structural changes found in the lungs were more severe and extensive than those previously described.[1–3]

Case reports

CASE 1

A male infant weighing 3400 g was born at full term after a normal pregnancy and delivery. The mother had received carbamezapine for epilepsy. There was no relevant family history. Apgar scores were 7 at 1 minute and 10 at 5 minutes. At 2 days of age the baby had two cyanotic episodes and was diagnosed as having a respiratory tract infection, although no pathogens were isolated. He was readmitted at the age of 20 days for investigation of failure to thrive. He had a further cyanotic episode, which was attributed to an *Escherichia coli* urinary tract infection. At 2 months of age it was noted that he became cyanosed when crying and feeding. He also had tachypnoea and sweatiness at rest. Arterial blood gas analysis while breathing air showed: pH 7·42, carbon dioxide tension 4·9 kPa, oxygen tension 4·7 kPa, and base excess 0·7. He was referred to the Brompton Hospital for investigation of suspected cyanotic heart disease.

On examination his weight had fallen to below the third centile for age. He was cyanosed and there was a prominent right ventricular impulse. The pulmonary component of the second sound was loud but there were no murmurs. His respiratory rate was 46 breaths/minute. The chest radiograph showed mild cardiomegaly and normal pulmonary vascular markings. The electrocardiogram showed a mean frontal QRS axis of +150° and right ventricular hypertrophy. The cross sectional echocardiogram showed normal anatomy of the heart with normal atrioventricular and ventriculoarterial connections. The right atrium was enlarged and the interatrial septum bowed from right to left. The right ventricle was grossly dilated with poor systolic function. The parasternal short axis view showed that the left ventricle was 'squashed', suggesting a high right ventricular pressure.

Cardiac catheterisation was carried out under general anaesthesia. The oxygen saturation in the aorta was 53%. The right ventricular pressure was 90/0–4 mm Hg with a simultaneous left ventricular pressure of 68/0–5 mm Hg. Using an estimated oxygen consumption of 150 ml/min/m^2 pulmonary vascular resistance was 24 units/m^2 in air and 10·5 units/m^2 in 100% oxygen.[4] Angiography showed poor right ventricular function but no intracardiac abnormalities. A diagnosis of persistent pulmonary hypertension of the newborn was made, and a pulmonary arterial line was left in.

The patient was extubated into headbox oxygen. The pulmonary artery pressure at this stage was 156/80 mm Hg with a systemic pressure of 80/30 mm Hg. Prostacyclin and adenosine were infused through the pulmonary arterial line. The patient was placed in a continuous subatmospheric (negative) extrathoracic pressure chamber and given 100% oxygen. None of these manoeuvres succeeded in lowering the pulmonary artery pressure appreciably, and it remained higher than the systemic pressure. On the day after cardiac catheterisation the patient had a cardiorespiratory arrest, which did not respond to intubation and standard resuscitative measures. Consent for necropsy was obtained.

CASE 2

A male infant weighing 3500 g was born at full term after a normal pregnancy and delivery. There was no relevant family history. Apgar scores were 8 at 1 minute and 9 at 5 minutes. He was noted to be cyanosed and breathless at 10 days of age. Arterial blood gas while breathing air showed: pH 7·19, carbon dioxide tension 3·2 kPa, oxygen tension 7·0 kPa, and base excess −17·9. He was transferred to the Hospital for Sick Children for investigation of suspected cyanotic heart disease.

On examination his weight had dropped to below the third centile and he was cyanosed and tachypnoeic. He had a prominent right ventricular impulse and the pulmonary component of the second heart sound was accentuated. There were no murmurs. The chest radiograph showed a heart of normal size with normal pulmonary vascular markings. The electrocardiogram showed a mean QRS axis of +140° and right ventricular hypertrophy. Cross sectional echocardiography showed normal anatomy of the heart with normal atrioventricular and ventriculoarterial connections. The interatrial septum was bowed from right to left. The right heart chambers were dilated and there was a small duct of no haemodynamic importance.

Cardiac catheterisation carried out under local anaesthesia at 4 weeks of age confirmed the echocardiographic findings and showed a pulmonary arterial pressure of 77/28 mm Hg with a simultaneous systemic arterial pressure of 75/36 mm Hg. Using an estimated oxygen consumption of 150 ml/min/m^2 the pulmonary vascular resistance was 15·6 units/m^2 in air and 15·0 units/m^2 in 100% oxygen. A diagnosis of persistent pulmonary hypertension of the newborn was made. At 5 weeks of age a Ladd's procedure for malrotation of the bowel was carried out, and the baby made an uneventful recovery. A week later he developed congestive cardiac failure and was treated with digoxin and frusemide.

A second cardiac catheterisation carried out at 2 months of age under general anaesthesia showed a saturation in the aorta of 78% and equal pulmonary artery and aortic pressures of 100/47 mm Hg. Pulmonary vascular resistance in air was 13·5 units/m^2 and in 100% oxygen 8·7 units/m^2. During cardiac catheterisation nifedipine, aminophylline, and isoprenaline all failed to reduce either the pulmonary arterial pressure or resistance. A pulmonary arterial line was left in. Prostacyclin was infused overnight through the pulmonary arterial line and continuous monitoring showed a slight reduction in pulmonary pressure to just below the systemic pressure. The baby continued to deteriorate, however, and hydralazine, tolazoline, further infusions of isoprenaline, and increased doses of prostacyclin had no effect. He died at 2·5 months of age. Consent for necropsy was obtained.

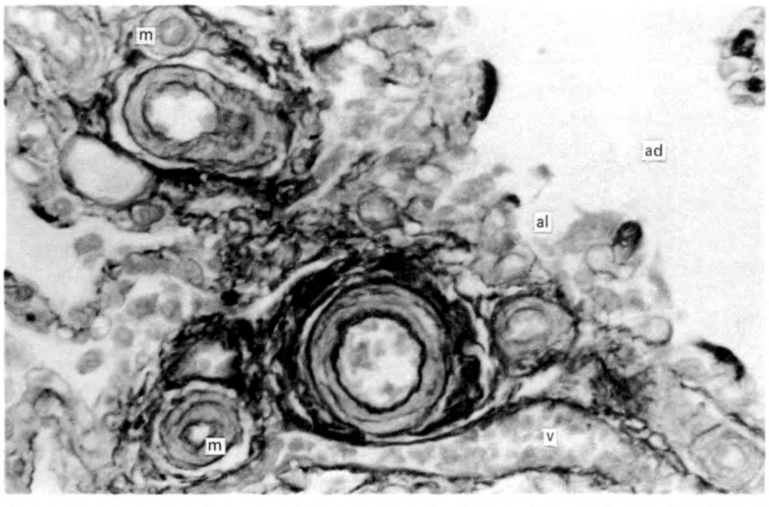


Figure 1 Photomicrograph (case 1). Small pulmonary arteries down to precapillary level are surrounded by a thick media (m) of muscle cells and an internal and external elastic lamina. The endothelial cells are rounded and reduce the size of the lumen. A pulmonary vein (v) larger than expected is close to the pulmonary arteries. Stain—elastic van Gieson, magnification×450, al=alveolus, ad=alveolar duct.

Histopathological findings

MACROSCOPIC FINDINGS

In both cases the right atrium and the tricuspid valve ring were dilated and the right ventricle was hypertrophied. Case 1 had subendocardial calcific streaks in the right anterior papillary muscle. The pulmonary trunk and central pulmonary arteries were dilated. The ductus arteriosus was closed in case 1 and persistent in case 2. The foramen ovale was patent in both cases, and in case 1 was membrane like with multiple perforations. The lungs looked normal, but mucopus was present in the large airways of case 2.

MICROSCOPIC STUDIES

Blocks of lung tissue were fixed in formol saline after intrabronchial inflation for light microscopic morphological studies, in a modified Bouin's solution for immunocytochemical examination of the innervation, or glutaraldehyde for electron microscopic studies. In each case at least five blocks of tissue were taken from different parts of the lung for microscopic examination. Morphometric analysis included measurements of percentage medial thickness of respiratory unit arteries and veins, of the size and structure of vessels accompanying identifiable airways, and of the number of small vessels in the alveolar region.[4]

Findings were similar in the two cases. Airway structure was normal. A normal number of alveoli had developed but their walls were thicker than normal as a result of an increase in the number and size of capillaries rather than an increase in the amount of connective tissue. The connective tissue septa and the collagenous sheets around the airways and blood vessels were prominent.

The preacinar and intra-acinar pulmonary arteries had grossly thickened walls caused by an increase in vascular smooth muscle. Mean percentage medial thickness of arteries 51–100 μm external diameter was 36·2% in case 1 and 39·2% in case 2 (normal 11·6%).[5] Muscle was increased in arteries of all size ranges and there was a thick muscle coat in small precapillary vessels lying in alveolar walls, which are normally not muscular in structure (fig 1). The muscle was so thick that it almost obliterated the lumen in many arteries. Further reduction in lumen size was the result of enlarged endothelial cells, which were chunky in outline. In some of the small vessels these cells totally occluded the lumen (fig 2). Mild cellular intimal proliferation was occasionally seen in the small muscular arteries proximal to the respiratory unit. This was cellular, loosely organised, and not obstructing the artery.

Pulmonary arteries in both the preacinar and acinar regions had normal external diameters in case 1 and increased diameters in case 2 because of the thick media. The number of small pulmonary arteries related to the number of alveoli were normal for age. The thickness of the walls of the pulmonary veins was increased. In veins that were 51–100 μm in external diameter the percentage wall thickness was 11·7% in case 1 and 7·5% in case 2 (normal 4·7%).[5] There were enlarged veins and lymphatics close to pulmonary arteries and airways in the intra-acinar region (fig 1).

Immunohistochemical studies using the general neuronal marker protein gene product 9·5 showed nerve fibres in the adventitia and primarily at the adventitial-medial border in all muscular arteries as far as the alveolar region. The neuropeptide tyrosine, a vasoconstrictive agent, was the predominant vasoactive peptide in these nerves (fig 3).

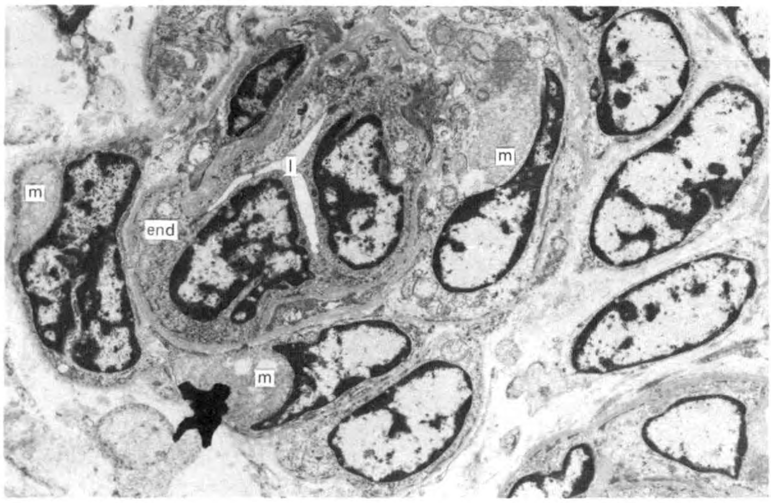
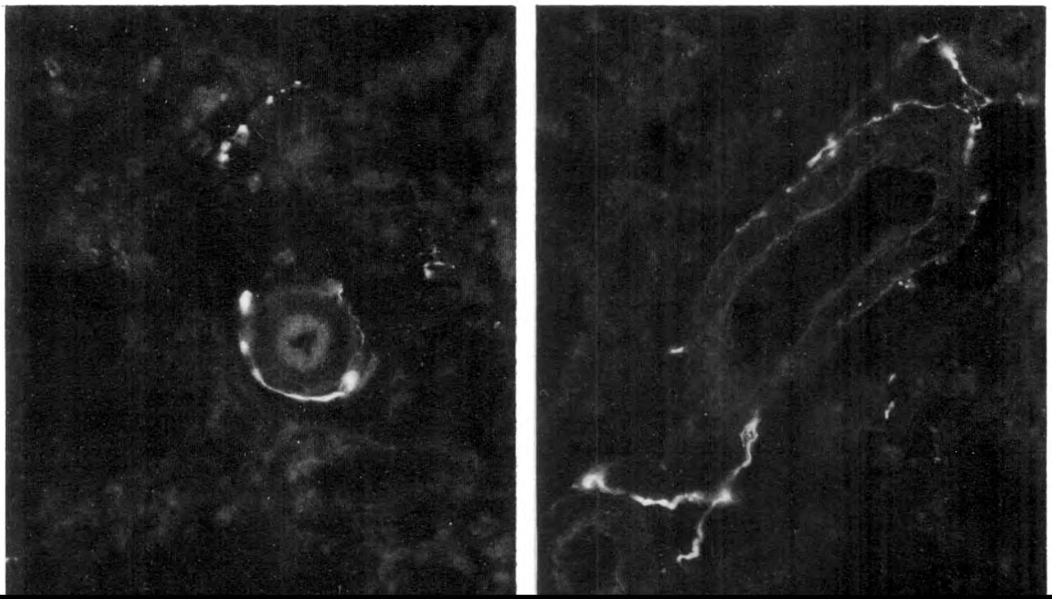


Figure 2 Electronmicrograph (case 2). A precapillary vessel has three chunky, tightly connected endothelial cells (end) that almost occlude the lumen (l). The vessel is surrounded by muscle cells (m). (Magnification×5666.)

Discussion

The absence of severe cyanosis at birth in these infants suggests that any right to left shunt must have been small and that pulmonary arterial pressure may have fallen, though probably not to normal. Cyanosis became apparent later as pulmonary arterial pressure rose and a right to left atrial shunt developed, the arterial duct having closed by the time of death of the first patient and being small in the second. The cyanosis may also have been partly the result of intrapulmonary shunting. This contrasts with ~~the usual presentation of persistent pulmonary~~ hypertension of the newborn in babies born at full term who characteristically present with severe cyanosis and hypoxaemia at birth.

The histopathological appearances were severe both in absolute terms and in relation to the age of the infants. The lungs were of normal size, with normal airway and alveolar development. In the normal newborn lung the percentage medial thickness of arteries less than 250 μm in diameter decreases rapidly during the first three days of life to approach the normal adult 'mature' medial thickness. This reduction in thickness is thought to be responsible for the rapid fall in resistance that occurs at birth,[5 6]



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and is associated with a thinning of the endothelial cells.[7] In the present cases it is probable that peripheral pulmonary arteries remained thick walled after birth in both infants and so pulmonary vascular resistance did not fall normally.

Examination of the structure of the arteries running along the peripheral airways showed extension of muscle distally along the arterial pathway so that most precapillary arteries had a completely muscular wall. In normal lungs at birth there are no muscular arteries beyond the level of the alveolar ducts and even in the adult most of the arteries in the alveolar region are non-muscular. Though there was no obvious reduction in the number of peripheral blood vessels, the increase in muscle cells and enlarged endothelial cells led to a reduced luminal cross sectional area. The thick enlarged appearance of the endothelial cells suggested that these vessels may not have been recruited into the pulmonary circulation at birth as they did not show the normal adaptive changes.[7] There was premature extension of the nerves to the periphery associated with the increase in muscle. In normal infants nerves do not extend far beyond the respiratory bronchiolar region.[8] These nerves were predominantly vasoconstrictive, and could have led to an increase in resistance.

None of the aetiological factors usually implicated in the pathogenesis of persistent pulmonary hypertension of the newborn (for example, birth asphyxia, polycythaemia, and hypoglycaemia) was present.[9] An increase in the muscularity of the small pulmonary arteries has been reported in cases where the ductus arteriosus has closed prematurely thereby increasing pulmonary artery pressure antenatally[10]; this possibility could be implicated in case 1 but not in case 2 in which there was a small persistent ductus arteriosus. The magnitude of the pulmonary vascular change and the thickness of the walls of the intra-acinar arteries (which in these cases exceeded the normal fetal amounts) suggests that at least some of the increased muscle developed before birth. This might have happened if the pulmonary circulation of these infants was abnormally sensitive to the hypoxic environment of fetal life, responding by excessive vasoconstriction and then by hypertrophy of muscle. Certainly after birth sensitivity to hypoxia varies considerably among individual infants.[11]

Alternatively, the increased muscularity may have represented a chance exuberant growth of normal muscle within the pulmonary circulation which, after birth, initiated a vicious circle to maintain arterial pressure leading to further hypertrophy of the arterial muscle. In the presence of pulmonary hypertension pericytes can rapidly differentiate into muscle cells, and in experimental hypoxia in rats and pigs do so within three days of exposure.[12 13]

It may be therefore that the fundamental abnormality in the infants described is the excessive muscularity antenatally of arteries less than 250 μm in diameter. Alternatively, the condition may have a pharmacological or neurological aetiology. The phospholipid leukotriene LTD4 seems to act as a pulmonary vasoconstrictor in newborn lambs,[14] and prostacyclin is a potent dilator of human fetal pulmonary arteries.[15] The production of leukotriene falls while that of prostacyclin rises in the perinatal period. Endothelial vasoconstrictors such as platelet derived growth factor are released during fetal life and stop being produced after birth.[16] Studies in porcine and human lungs have shown that sympathetic nerves contain vasoconstrictor neurotransmitters.[17] In man the density of nerve fibres is low in the arteries of the respiratory unit at birth but may increase during childhood. These nerves are predominantly vasoconstrictor in effect and an increase in the number, distribution, or function of these vasomotor nerves may cause excessive pulmonary vasoconstriction. This may be responsible for the persistent pulmonary hypertension in these cases as there was extensive innervation in the small muscular peripheral arteries. The premature innervation of the muscularised peripheral arteries may be primary or secondary. Nerves can have a trophic affect on muscle cells,[18] but increased muscularity may lead to increased innervation. There is no evidence of a link between maternal ingestion of carbamezapine (case 1) and the development of persistent pulmonary hypertension of the newborn.

Whatever the aetiology, the effect of a reduction in the diameter of the lumen of patent arteries, together with an increase in thickness of the walls, was to increase resistance by decreasing the cross sectional area of the pulmonary vascular bed. An increase in both the thickness of the muscle coat and the length of the muscularised pathway also increased the capacity to vasoconstrict. Even the smallest precapillary arteries had muscle cells in their walls and would be able to have constricted. Thus vasoconstriction seems to be an important mechanism leading to persistent pulmonary hypertension of the newborn.

The cases described illustrate the extreme pathological changes that may develop in persistent pulmonary hypertension of the newborn. The association between structure and function in neonatal pulmonary hypertension is complex and unclear. Studies of the association between vascular smooth muscle maturation, contractility, and innervation will—we hope—help to determine the aetiology and subsequently the treatment of this disease.

We thank Dr J Wharton for figure 3.

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Trends in preterm survival and incidence of cerebral haemorrhage 1980–9

R W I Cooke

Abstract

The annual survival rates and incidence of cerebral haemorrhage in 2618 preterm infants of 34 weeks' gestation or less were examined in one referral centre over a 10 year period from January 1980 to December 1989. Survival was independently related to weight, gestation, sex, and inborn delivery. When these variables had been taken into account, survival was 56% greater at the end of the decade compared with 1980. The incidence of cerebral haemorrhage (diagnosed by cranial ultrasound scanning) was related to birth weight, gestation, sex, inborn delivery, and caesarean section, but there was no significant trend in the incidence with time. Rates of caesarean section in this group increased from 31% in 1980 to over 50% more recently. Haemorrhage affecting the brain parenchyma was related to gestation and inborn delivery, and showed a small but significant decline over time. The lack of association between changes in survival rates and rates of cerebral haemorrhage may indicate that factors associated with both neonatal mortality and the incidence of cerebral haemorrhage may not be causally related as previously assumed.

There have been many reports describing improvements in survival of preterm infants over the past 20 years, and national statistics have shown a decline in birthweight specific mortality of low birthweight groups.[1] Such improvements usually accompanied the introduction of intensive care techniques for low birthweight infants, rather than occurring in centres where such techniques already existed. There has been an increasing awareness of the problems associated with intracranial haemorrhage in preterm infants, and the hope was that the incidence of this potentially disabling disorder had also decreased as mortality was reduced; several reports claimed that this had occurred.[2–4] This paper describes the experience of a large neonatal intensive and special care unit in the United Kingdom by examining trends in neonatal mortality and cerebral morbidity over the past decade.

Table 1 Variables used in the analyses

- Birth weight (g)
- Gestational age (weeks)
- Singleton/multiple birth
- Vaginal delivery/caesarean section
- Inborn/outborn delivery
- Sex
- Survival to discharge
- Grade of periventricular haemorrhage

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Patients and methods

All infants of 34 weeks' gestation or less who were admitted to the Mersey regional neonatal intensive care unit and special care unit over a 10 year period were included in the study. The variables analysed are listed in table 1. Cranial ultrasonography has been used to diagnose cerebral lesions since late in 1979, and all infants weighing less than 1500 g at birth, and most larger infants receiving intensive care, were regularly examined. Data have been recorded prospectively since January 1980 to evaluate ultrasonographic diagnosis, and the data used in this paper was abstracted from this.

Ultrasound scans were not performed routinely on larger infants who were admitted only for special care, and who did not have respiratory problems or birth asphyxia. A simple grading system for cerebral haemorrhage was used to classify the early lesions: none, subependymal haemorrhage, intraventricular haemorrhage, and parenchymal haemorrhage. The last category includes both haemorrhagic infarction and venous infarction as they cannot reliably be distinguished. A more complex system of grading was not used, nor were later parenchymal lesions such as cystic periventricular leucomalacia included, because the interpretation of these lesions has been modified over the decade. Only data relating to the overall rates of haemorrhage and of parenchymal haemorrhage are reported here. Survival was defined as alive at the time of discharge from the unit. Deaths because of chromosomal and other lethal congenital abnormalities were excluded from the analysis of survival rates, but not from the other analyses.

Trends in survival and haemorrhage rates were tested using χ^2 for trend. Univariate analysis was by the χ^2 test or unpaired Student's t test. Logistic regression was then used to test for the independent effects of the variables shown in table 1 on survival and the incidence of haemorrhage. Each year after 1980 was also entered into the logistic regressions as an independent variable to test for differences in rates of survival and haemorrhage in that year relative to the baseline of 1980 after other variables had been taken into account. The effect of categorical variables and year of birth on rates of survival and haemorrhage were then derived from the logistic regression odds ratios with their 95% confidence intervals (CI).

The odds ratio is the change in likelihood of an event occurring if a particular variable or category of variable is present. A ratio of 1·5 indicates that the probability of occurrence is increased by 50%. The odds ratio is an estimate, and the 95% CI indicate the range within which one can be 95% certain that the true value will lie. If these limits do not encompass 1, it is accepted that the odds ratio is significantly different from an even chance, and that a true difference exists.

Results

SURVIVAL

During the decade 1 January 1980 to 31 December 1989, 2662 infants of 34 completed weeks of gestation or less were admitted to the Mersey regional neonatal intensive care and special care unit at Liverpool Maternity Hospital. Forty four died of lethal chromosomal or other abnormalities. Of the remaining 2618 infants, 486 (18·6%) died before discharge home. A significant trend to improved survival in more recent years was seen for all infants, for infants of less than 28 weeks' gestation, and for infants weighing less than 1500 g at birth (table 2). Univariate analysis also showed that survival was related to sex, gestation, birth weight, whether the infant was inborn, and whether delivery was by caesarean section (table 3). A number of these variables could have contributed to the apparent observed improvement in survival, although only caesarean section showed a significant trend related to year of birth (table 4). Logistic regression analysis showed that weight, gestational age, sex, and place of birth were independent variables that were significantly related to survival, as was year of birth. The odds ratio for survival in any one year compared with 1980 was significantly better than 1 in 1983 and from 1985 onwards when all infants were considered (fig 1). When only infants under 1500 g were studied, survival was significantly better in 1983 and from 1986 onwards, and when infants of less than 28 weeks' gestation were considered, survival was significantly improved compared with 1980 only in 1988 and 1989. Caesarean section was not independently related to survival in any group, inborn delivery only to the cohort as a whole, and multiple pregnancy only to infants of less than 28 weeks' gestation.

Table 2 Percentage trends in annual survival rates in infants of 34 weeks' gestation and under, in infants of less than 28 weeks' gestation, and of infants who weighed less than 1500 g at birth. Figures in parentheses are numbers of infants

Year	*Infants of ≤34 weeks' gestation (n=2618)*	*Infants of <28 weeks' gestation (n=537)*	*Infants who weighed <1500 g (n=1470)*
1980	75·1 (209)	41·0 (39)	61·2 (121)
1981	77·2 (268)	44·1 (59)	68·1 (166)
1982	80·9 (278)	38·0 (50)	68·8 (144)
1983	83·0 (311)	46·0 (63)	75·3 (178)
1984	81·3 (273)	38·3 (47)	66·9 (142)
1985	81·9 (276)	47·2 (53)	67·8 (149)
1986	83·8 (277)	55·2 (58)	78·8 (160)
1987	82·7 (254)	45·6 (57)	72·9 (155)
1988	82·9 (217)	64·8 (54)	74·2 (124)
1989	84·3 (255)	61·4 (57)	74·8 (131)
χ^2 for trend	8·20	10·36	7·26
p Value	0·004	0·001	0·007

Table 4 Percentage trend in the annual incidence of caesarean sections among all infants. Figures in parentheses are numbers of infants

Year	*Vaginal delivery (n=1473)*	*Caesarean section (n=1189)*
1980	69·0 (149)	31·0 (67)
1981	61·1 (165)	38·9 (105)
1982	61·1 (173)	38·9 (110)
1983	59·4 (188)	40·3 (127)
1984	48·9 (135)	51·1 (141)
1985	52·0 (146)	48·0 (135)
1986	43·6 (123)	56·4 (159)
1987	57·1 (148)	42·9 (111)
1988	55·9 (124)	44·1 (98)
1989	47·3 (122)	52·7 (136)
χ^2 for trend	27·4	
p Value	0·0001	

CEREBRAL HAEMORRHAGE

Of the 2662 infants admitted, 2313 (86·9%) had cranial ultrasound scans. All the infants who weighed less than 1500 g at birth or were of less than 28 weeks' gestation were scanned. When all infants were considered, the overall incidence of haemorrhage did not change over the decade (table 5). There was a small but significantly decreasing trend in the incidence of parenchymal haemorrhage (table 6). In infants weighing less than 1500 g at birth there was a trend towards an increasing overall incidence of all types of haemorrhage, but no change in that of parenchymal lesions. In infants of less than 28 weeks' gestation there were no significant trends in either direction. Logistic regression analysis showed that weight, gestation, caesarean section, sex, and inborn delivery were independently related to all grades of haemorrhage (table 7), and gestation and inborn deliveries were related to the incidence of parenchymal haemorrhages (table 8). After other variables had been taken into account, the incidences of both haemorrhage and parenchymal haemorrhage were higher in 1981 and 1982, and that of parenchymal haemorrhage in 1986, 1988, and 1989, but there was no consistent

Table 3 Univariate analysis of variables relating to survival, together with odds ratios and 95% CI derived from logistic regression

	Infants who survived (n=2132)	*Infants who died (n=486)*	*p Value*	*Odds ratios (95% CI)*
Mean (SD) birth weight (g)	1546 (481)	1035 (396)	<0·0001	1·14 (1·08 to 1·21)/250 g
Mean (SD) gestation (weeks)	30·7 (2·5)	27·3 (2·5)	<0·0001	1·20 (1·15 to 1·25)/week
No (%) singleton births	1675 (81·5)	380 (18·5)	>0·05	1·01 (0·88 to 1·17) for multiple births
No (%) multiple births	457 (81·2)	106 (18·8)		
No (%) inborn deliveries	1553 (84·1)	294 (15·9)	<0·0001	1·13 (1·00 to 1·28) for inborn deliveries
No (%) outborn deliveries	579 (75·1)	192 (24·9)		
No (%) vaginal deliveries	1133 (78·0)	320 (22·0)	<0·0001	0·94 (0·89 to 1·08) for vaginal deliveries
No (%) caesarean sections	999 (85·8)	166 (14·2)		
No (%) male	1165 (79·4)	302 (20·6)	<0·002	0·76 (0·68 to 0·86) for male sex
No (%) female	967 (84·0)	184 (16·0)		

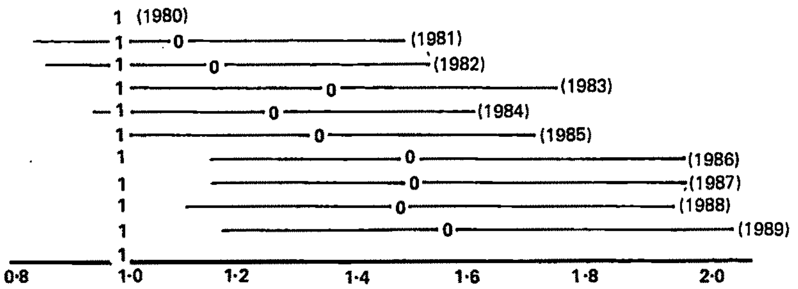

Figure 1 Odds ratio (with 95% CI) for survival in each year compared with 1980.

Table 5 Percentage trends in annual incidence of any grade of periventricular haemorrhage in infants of 34 weeks' gestation and under, in infants of less than 28 weeks' gestation, and in infants who weighed less than 1500 g at birth. Figures in parentheses are numbers of infants

Year	*Infants of ≤34 weeks' gestation (n=2313)*	*Infants of <28 weeks' gestation (n=546)*	*Infants who weighed <1500 g (n=1489)*
1980	39·1 (138)	53·7 (41)	39·7 (126)
1981	43·1 (225)	74·6 (59)	53·6 (168)
1982	41·0 (234)	67·3 (52)	47·3 (148)
1983	27·9 (276)	57·1 (63)	37·4 (179)
1984	32·6 (242)	70·2 (47)	45·4 (141)
1985	30·7 (254)	60·4 (53)	43·3 (150)
1986	50·4 (260)	74·6 (59)	61·3 (163)
1987	38·8 (245)	70·0 (60)	49·7 (159)
1988	40·9 (210)	72·7 (55)	59·3 (123)
1989	41·9 (229)	66·6 (57)	55·3 (132)
χ^2 for trend	1·90	1·39	10·81
p Value	0·16	0·23	0·001

Table 6 Percentage trends in annual incidence of parenchymal haemorrhage in infants of 34 weeks' gestation and under, in infants of less than 28 weeks' gestation, and in infants who weighed less than 1500 g at birth. Figures in parentheses are numbers of infants

Year	*Infants of ≤34 weeks' gestation (n=2313)*	*Infants of <28 weeks' gestation (n=546)*	*Infants who weighed <1500 g (n=1489)*
1980	10·1 (138)	9·8 (41)	9·5 (126)
1981	16·9 (225)	37·3 (59)	22·0 (168)
1982	14·1 (234)	34·6 (52)	19·6 (148)
1983	8·3 (276)	19·0 (63)	11·2 (179)
1984	9·9 (242)	23·4 (47)	15·6 (141)
1985	9·4 (254)	20·8 (53)	13·3 (150)
1986	13·5 (260)	33·9 (59)	19·6 (163)
1987	6·9 (245)	18·3 (60)	10·1 (159)
1988	8·1 (210)	14·5 (55)	13·0 (123)
1989	10·5 (229)	19·3 (57)	15·9 (132)
χ^2 for trend	4·94	2·10	0·6
p Value	0·026	0·147	0·43

relationship with time. Similar results were seen for cerebral haemorrhage over time in infants weighing less than 1500 g at birth and of less than 28 weeks' gestation.

Discussion

Survival of preterm infants during the past decade has consistently improved. As full intensive care has been given to all infants admitted without potentially lethal malformations over this period of time, any improvment in outcome is likely to be related to changes in the population of infants treated, or to the combined effects of the many minor changes in management that have occurred. Analysis of the variables examined showed no consistent trend with time except for an increase in the proportion of caesarean sections.

When all the variables were entered into a logistic regression, caesarean section was no longer significantly associated with improved survival, although birth in more recent years was still associated with improved survival. Similar effects were noted for infants weighing less than 1500 g at birth, and those of less than 28 weeks' gestation, although survival was significantly better only in the most recent years. This improvement in survival is likely to be real rather than related to population changes.

The annual incidence of cerebral haemorrhage over the decade showed a different pattern. When all infants were considered, no consistent trend emerged except for a small but significant decrease in the number of parenchymal haemorrhages. Infants weighing less than 1500 g at birth showed an overall trend to an increased incidence of all haemorrhages, but not to parenchymal haemorrhages alone. As expected, logistic regression analysis showed correlations between haemorrhage and variables such as gestational age and weight, inborn delivery, sex, and caesarean section, but no variable was consistently correlated with the incidence of haemorrhages of different degrees or in different groupings. Similarly, some individual years showed a significantly greater incidence of haemorrhage than 1980, but no consistent trend emerged.

A number of reports have suggested that the incidence of cerebral haemorrhage among preterm infants is decreasing, but many of the observations are confined to a short period of time or to small numbers. Szymonowicz *et al*

Table 7 Univariate analysis of variables relating to any grade of periventricular haemorrhage, with odds ratios and 95% CI derived from logistic regression

	Infants without periventricular haemorrhage (n=1424)	*Infants with any grade of periventricular haemorrhage (n=889)*	*p Value*	*Odds ratios (95% CI)*
Mean (SD) birth weight (g)	1492 (477)	1169 (402)	<0·0001	0·94 (0·90 to 0·98)/250 g
Mean (SD) gestation (weeks)	30·5 (2·5)	28·2 (2·5)	<0·0001	0·87 (0·84 to 0·90)/week
No (%) singleton births	1109 (77·9)	687 (77·3)	>0·05	1·03 (0·92 to 1·16) for multiple births
No (%) multiple births	315 (22·1)	202 (22·7)		
No (%) inborn deliveries	1039 (73·0)	533 (60·0)	<0·0001	0·78 (0·71 to 0·87) for inborn deliveries
No (%) outborn deliveries	385 (27·0)	356 (40·0)		
No (%) vaginal deliveries	706 (49·6)	560 (62·9)	<0·0001	0·90 (0·81 to 0·99) for caesarean sections
No (%) caesarean sections	718 (50·4)	329 (37·1)		
No (%) male	765 (53·7)	520 (58·5)	<0·02	1·18 (1·07 to 1·29) for male sex
No (%) female	659 (46·3)	369 (41·5)		

Table 8 Univariate analysis of variables relating to parenchymal haemorrhage, with odds ratios and 95% CI derived from logistic regression

	Infants without parenchymal haemorrhage (n=2064)	*Infants with parenchymal haemorrhage (n=249)*	*p Value*	*Odds ratios (95% CI)*
Mean (SD) birth weight (g)	1404 (476)	1070 (361)	<0·0001	0·93 (0·86 to 1·003)/250 g
Mean (SD) gestation (weeks)	29·9 (2·7)	27·5 (2·3)	<0·0001	0·87 (0·83 to 0·91)/week
No (%) singleton births	1596 (77·3)	200 (80·3)	>0·05	
No (%) multiple births	468 (22·7)	49 (19·7)		0·92 (0·77 to 1·11) for multiple births
No (%) inborn deliveries	1438 (69·7)	134 (53·8)	<0·0001	
No (%) outborn deliveries	626 (30·3)	115 (46·2)		0·76 (0·66 to 0·87) for inborn deliveries
No (%) vaginal deliveries	1109 (53·7)	157 (63·0)	<0·006	
No (%) caesarean sections	955 (46·3)	92 (37·0)		1·09 (0·94 to 1·29) for caesarean sections
No (%) male	1142 (55·3)	143 (57·4)	>0·05	
No (%) female	922 (44·7)	106 (42·6)		1·07 (0·92 to 1·23) for male sex

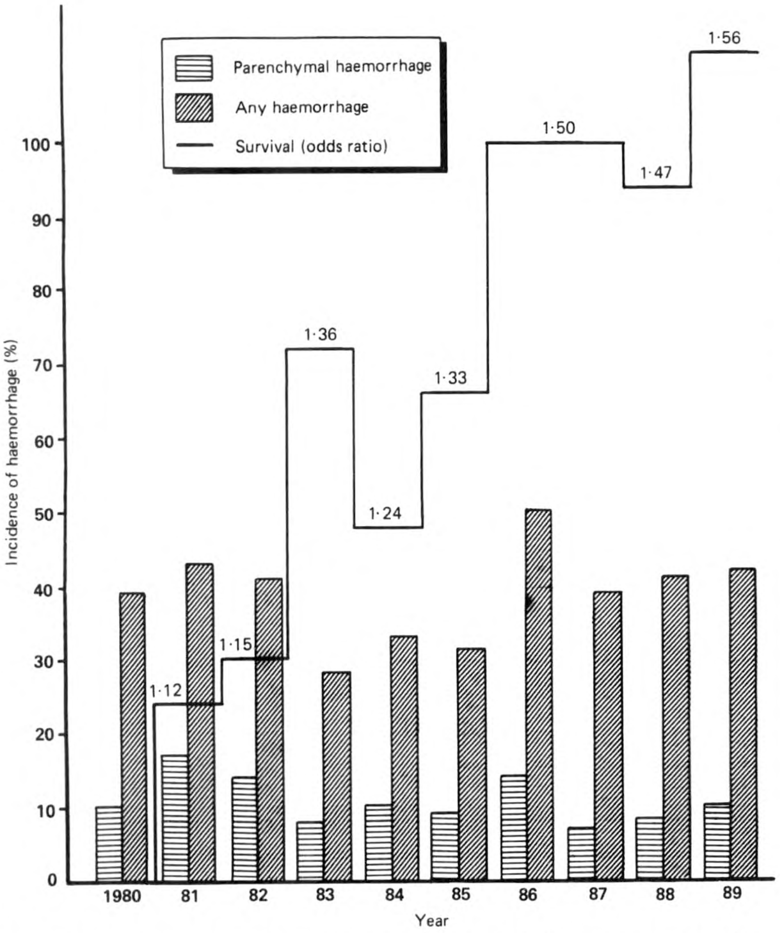

Figure 2 Incidence of haemorrhage 1980–9. Superimposed on the histogram are the odds ratios for survival in each year compared with 1980.

compared a group of 100 infants who weighed less than 1250 g at birth and who were born during 1983–4 with 50 infants born in 1982 and concluded that the halving of the incidence of haemorrhage that they found was the result of changes in management over that period.[2] Survival was also better in the second cohort.

Philip *et al* compared the incidence of haemorrhage among four two year cohorts of infants of 34 weeks' gestation or less who were admitted to a single unit between 1980 and 1987.[3] There were significant trends in a reduction in incidence in the group as a whole and among those weighing less than 1500 g at birth. Infants who died early were excluded from scanning. The authors attributed the improvements to better neonatal management.

In the light of the consistently improving survival over a 10 year period seen in this study, it is somewhat surprising to note the lack of reduction in the incidence of cerebral haemorrhage (fig 2). Could other changes that we did not examine have masked a real change in the incidence of haemorrhage? The infants most intensively studied by ultrasound scanning were those weighing less than 1500 g at birth. Improvements in the quality of resolution of scans, and greater interest in more minor lesions in recent years, could have produced a rise in diagnoses of smaller haemorrhages over the period, so giving an overall apparent rise in incidence. The incidence of serious parenchymal haemorrhages did not alter, however, and these lesions are the least likely to be overdiagnosed.

Our policy in recent years of not admitting otherwise well infants weighing more than 2000 g to the unit could have increased the apparent vulnerability of the population in the unit at the more mature end, concealing an actual fall in the incidence of haemorrhage. Factors such as a change in population in terms of weight, gestation, inborn delivery, sex, multiple births, and caesarean section were considered in the logistic regression, and did not affect the conclusions of the simpler analyses. Differences in the severity of disease may have been independent of these variables and consequently were not allowed for.

Alternatively, there may indeed have been no real change in the incidence of haemorrhage. Szymonowicz *et al* compared two small cohorts from two separate times. Although the change in incidence that they found was substantial, equally large changes from year to year in both directions were seen in the present study. Batton *et al* described a reduction in the incidence of haemorrhage in their unit from 1981 to 1983, but a reversal of this trend in 1984.[4] The unaccounted variance in incidence from year to year means that a long term view of such changes must be taken before robust conclusions can be drawn. The use of historical controls in therapeutic intervention studies is clearly fraught with problems, and only randomised trials can hope to avoid these.

If there has been no real reduction in the incidence of haemorrhage despite improved survival, should we be surprised? It has been assumed that the antecedents of haemorrhage are largely the diseases such as hyaline membrane disease that are also related to preterm mortality. A recent commentary on hyaline membrane disease and intraventricular haemorrhage pointed out that in a meta-analysis of the results of trials of surfactant treatment of hyaline membrane disease, the mortality and severity were considerably reduced, though there was no significant effect on the incidence of cerebral haemorrhage.[5] Although a few trials showed a reduction in the incidence of haemorrhage, this was no more than might have been expected by chance. Such findings call into question the relationship between diseases such as hyaline membrane disease and intraventricular haemorrhage, and whether it is causal or merely simple association. Furthermore, the reduction in perinatal mortality in low birthweight infants during the past 20 years has been accompanied by an increase rather than a decrease in later morbidities such as cerebral palsy.[6]

Though a number of therapeutic interventions have been shown in randomised trials to reduce haemorrhage in selected subgroups, their effect on the whole population over the last decade has not been obvious, despite a continued improvement in survival.[7] The causes of cerebral haemorrhage in preterm infants may not be as closely related to perinatal factors as previously thought.

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Survival and place of treatment after premature delivery

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Abstract

In a one year prospective study in the Trent region we examined the short term outcome (survival to discharge) of all infants who required admission to a baby care unit. Infants of less than or equal to 28 weeks' gestation who received all their perinatal care in one of five large centres (each providing more than 600 ventilator days/year) showed significantly better survival rates than infants electively treated throughout their entire course at one of the 12 smaller units (34 survivors from 65 infants (52%) compared with eight survivors from 37 infants (22%). These differences occurred despite the elective transfer of many of the sickest infants from the smaller units to the larger. Differences in survival between more mature infants were not significant. These results support the policy that there should be a more centralised neonatal service for those infants at or below 28 weeks' gestation.

Neonatal intensive care is expensive,[1] and potentially hazardous,[2] but many paediatricians feel that it has made a considerable contribution to the improvements in perinatal and infant mortality in the last two decades.[3 4] Others have reservations about the rapid growth of the specialty.[5 6]

This controversy has arisen because the value of neonatal intensive care has never been tested in a controlled trial, and few clinicians would now consider that such a trial was ethical. Similarly, major treatment measures in neonatal intensive care (such as artificial ventilation for

[redacted]

the study the baby units could be divided into two categories:firstly, there were five intensive care units which regularly carried out intensive care procedures such as artificial respiratory support, and secondly, there were 12 special care units with variable capacities for intensive care. The former group conformed to the guidelines of the Royal College of Physicians for either regional or subregional perinatal centres.[10]

All the large units had at least one consultant with an interest in neonatal medicine, all had 24 hour middle grade medical cover, and all ran specialist courses in neonatal nursing. Each unit carried out at least 500 days of ventilation annually (range 605–1590 days). Of the 12 smaller units four aimed to provide intensive care for most of the infants born in the hospital, and the remainder planned to transfer most cases needing intensive care. Most but not all of these units had a consultant with an interest in neonatal care, three had 24 hour middle grade medical cover (none resident on site), and none ran a course in neonatal nursing. Ten of the special care units had equipment available to provide long term artificial ventilation, the commonest intensive care procedure. None of the 12 units provided more than 500 days of ventilation annually (range 5–420 days).

The study took place between 1 February 1987 and 31 January 1988. Data were collected on every admission to each of the 17 baby care units by one of four observers (two doctors and two nurses); we recorded place of booking, place of birth, birth weight, gestation, treatment, and outcome (discharge or death).

No infant referred for intensive care was refused, although on 14 occasions this required

Table 1 All babies studied according to where they received their perinatal care, gestational age, and mortality

Group	*All perinatal care in large units*	*All perinatal care in small units*	*Antenatal transfers to large units*	*Postnatal tranfers to large units*
All admissions:				
Total No	1443	2500	117	192
No (%) deaths	95 (7)	77 (3)	23 (20)	46 (24)
Babies of >32–≤ 34 weeks' gestation				
Total No	268	345	17	28
No (%) deaths	4 (2)	5 (2)	1 (6)	5 (18)
Babies of >30–≤ 32 weeks' gestation				
Total No	174	170	30	31
No (%) deaths	9 (5)	11 (6)	3 (10)	3 (10)
Babies of >28–≤ 30 weeks' gestation				
Total No	97	30	19	25
No (%) deaths	17 (18)	2 (7)	8 (42)	9 (36)
Babies of ≤ 28 weeks' gestation				
Total No	65	37	35	47
No (%) deaths	31 (48)	29 (78)	14 (40)	19 (40)

infants born inside the region. These were divided into four groups: babies who received all their perinatal care in one of the five hospitals with full intensive care facilities, those who received all their perinatal care in one of the 12 hospitals not designated as having full intensive care facilities, those transferred antenatally from a small hospital to a large hospital, and those transferred after delivery from a small hospital to a large hospital. The distribution by gestational age and survival of infants in the four groups is shown in table 1.

Comparing infants treated in the large hospitals with those treated in the small ones, several points arise.

Survival among all admissions (irrespective of gestational age) was apparently better for infants in the smaller units. This is not an appropriate comparison, however, because the special care units operated a completely different admission policy that lead to the admission of a large number of mature infants for treatments other than intensive care (infants >34 weeks' gestation, no intensive care: larger units 756, 56% of all admissions; smaller units 1864, 77% of all admissions). An increased number of lethal malformations was also included in the deaths on large units (33 compared with 24). Other malformations that required operation carrying a high mortality (for example, diaphragmatic hernia) were transferred out of the small units and are included in columns 3 and 4 of table 1.

Survival of infants of >32 but ≤ 34 weeks' gestation, >30 but ≤ 32 weeks' gestation, and >28 but ≤ 30 weeks' gestation was not significantly different between the two types of unit ($p=0{\cdot}65$, $0{\cdot}77$, and $0{\cdot}12$, respectively, Fisher's exact test). Relative odds (95% CI) of dying (small units compared with large units) in these gestational age groups were:0·97 (0·25 to 3·70), 1·26 (0·50 to 3·23), and 0·34 (0·07 to 1·61), respectively.

Survival of infants ≤ 28 weeks' gestation was significantly better for infants treated in designated intensive care units (34 survivors from 65 infants compared with eight survivors from 37 infants, χ^2 7·94, 1 df, $p<0{\cdot}005$; relative odds (95% CI) of dying (small units compared with large units) were 3·98 (1·55 to 10·18)). Improved survival was not related to an excess of congenital abnormalities among infants in special care units.

In addition, the two groups of infants were compared with a scoring system designed to predict outcome based on the following variables: birth weight, gestation, respiratory distress at birth, cephalic or breech presentation, Apgar scores at 1 and 5 minutes, and multiple pregnancy.[12] The most important components of this score are respiratory distress at birth, birth weight, and Apgar score at 5 minutes. Only the incidence of respiratory distress was significantly different between the two types of unit indicating a worse potential for infants from larger units. Large units had 62 of 65 with respiratory disease compared with small units that had 28 out of 37, $p<0{\cdot}01$; mean (SD) birth weight in large units was 970 (26) g and in small units 930 (28) g, $p>0{\cdot}05$; and mean (SD) 5 minute Apgar scores in large units were 7 (2), range 1–10 and in small units 6 (3), range 1–10, $p>0{\cdot}05$. There were no significant differences between any of the other variables.

Despite being particularly high risk groups (confirmed by risk scoring) infants of ≤ 28 weeks' gestation who were transferred either antenatally or postnatally to large units showed improved survival compared with infants who remained in special care nurseries. Antenatal transfers ≤ 28 weeks' gestation: 21 survivors from 35 infants compared with eight survivors from 37 infants, $\chi^2=9{\cdot}48$, 1 df, $p<0{\cdot}002$; relative odds of dying (95% CI) (transferred compared with not transferred 5·44 (1·89 to 15·62). Postnatal transfers at ≤ 28 weeks' gestation: 28 survivors from 47 infants compared with eight survivors from 37 infants, $\chi^2=11{\cdot}31$,

Table 2 Babies who received all their perinatal care in large or small units divided according to birth weight and mortality

	All perinatal care in large units	*All perinatal care in small units*
All babies		
Total No	1443	2500
No (%) deaths	95 (7)	77 (3)
Babies weighing 2000–2500 g		
Total No	289	603
No (%) deaths	3 (1)	10 (2)
Babies weighing 1500–2000 g		
Total No	295	355
No (%) deaths	7 (2)	9 (3)
Babies weighing 1000–1500 g		
Total No	146	90
No (%) deaths	20 (14)	11 (12)
Babies weighing <1000 g		
Total No	58	35
No (%) deaths	33 (57)	26 (74)

1 df, $p<0\cdot0008$; relative odds of dying (95% Cl) (transferred compared with not transferred) 5·34 (1·97 to 14·45).

Reviewing the same data by birth weight shows the same trends, but differences in survival are not significant (table 2). This is to be expected as in general mature growth retarded infants do well without the severe problems related to immaturity. Some of these infants will have been included in the low birthweight groups.

Discussion

These data indicate that infants of 28 weeks' gestation or less show improved survival when they are treated in recognised neonatal intensive care units compared with infants who are electively treated in smaller units. This difference is particularly important, as many of the sickest infants were transferred from the smaller units and this was confirmed by risk scoring. There was no indication that the smaller units electively retained an excess of infants unlikely to survive for terminal care. It was in the larger units that a policy of offering terminal care to very immature infants away from the labour ward was more firmly established. The mechanism for the improved survival has not been shown.

No information is available about rates of handicap. Clearly this is important and will be considered in a further study. The limited number of survivors of 28 weeks' gestation or less, however, means that a study of several health regions will be required to obtain sufficient data for comparison. Without these data our findings must be interpreted with caution.

In a recent publication that was broadly critical of neonatal intensive care, attention was focused on artificial respiratory support as the essential element.[6] This seems inappropriate as many aspects of perinatal care have evolved in the last 20 years to produce what we now call neonatal intensive care. Any advantages that large centres have are likely to relate both to obstetric and neonatal experience with high risk deliveries rather than individual treatments. The growth and dissemination of knowledge in neonatal care has clearly produced good short term survival figures for infants of more than 28 weeks' gestation in all units.

These findings are of importance in the futures planning of neonatal care. Although centralisation of neonatal care has been advocated there has been no direct evidence to support such a move in the United Kingdom,[10] although data similar to our own are available from the United States and The Netherlands.[13 14] Our data indicate that survival of infants of ≤28 weeks' gestation is better when they are cared for in designated centres. It seems unlikely that future studies will be able to separate the differences in contributions of medical care (obstetric and neonatal), nursing care (neonatal and midwifery) and type of equipment between the two types of unit in a controlled manner. Based on the criteria of improved survival alone, therefore, these findings indicate that the intensive care of infants delivered at ≤28 weeks' gestation and the perinatal care of pregnancies identified as high risk should be concentrated in units: that carry out at least 500 days of neonatal ventilation/year; that have at least one consultant with a special interest in the newborn, and that have continuous middle grade medical cover; that have a high level of nursing expertise and training in neonatal care; and where obstetric care for high risk deliveries is well established.

For infants of more than 28 weeks' gestation there is no indication from these data that care should take place in designated centres. A comparison between the two types of unit of these more mature babies with similar diseases has not been possible. This might be achieved in a study of several regions that would provide sufficiently large numbers to allow matching for severity of disease.

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Commentary

Provision of neonatal intensive care has been singled out by the Royal College of Physicians and the National Audit Office as an area for improvement in services,[1 2] and the chief executive of the NHS has made it a priority for regions and districts to review their maternity and neonatal services with a view to further reductions in mortality.[3] Between 1980 and 1986, in England, the number of cots for neonatal intensive care more than doubled, and birthweight specific perinatal and neonatal mortality fell in all categories of birth weight.

There are differences, however, in mortality rates for low and very low birthweight babies among health regions.[4] This may reflect differences in the social and economic factors that affect pregnancy outcomes, but there are also differences in the funding and organisation of neonatal care. In particular, regions vary in the amount of centralisation of neonatal intensive care, and in the arrangements that are made for transfer of babies.[5] The problem is to decide whether and how different organisation of neonatal services within a region can improve neonatal outcomes.

Field *et al* present data about the mortality among babies in the Trent region who were admitted to neonatal units categorised into two groups by their capabilities to provide intensive care. They conclude that, for babies of more than 28 weeks' gestation, mortality was not related to admission to units with different degrees of services. For babies of less than or equal to 28 week gestations they did find that there was a significantly higher mortality among babies admitted to smaller neonatal units and not subsequently transferred to a regional unit.

This finding raises questions both of interpretation of the results and of implications on policy. The conclusion that babies born at gestations of 28 weeks or less should receive neonatal care in the larger referral centres may be misleading. Apart from access to different types of care, there may be other differences among the babies treated in the different types of neonatal unit. In their analysis, Field *et al* recognise that they had not done and could not do a randomised trial. As a result, they may not have controlled adequately for the possibility of unmeasured differences among the babies receiving different types of care. This bias may arise if there were babies in the smaller units who were born too quickly for transfer to be arranged before they were born, or after delivery if the baby was thought to be too immature or too sick to survive transport. Although this decision is sometimes made independently of the regional centre, many such decisions are made after at least a telephone consultation with the regional unit.[5 6]

If differences in mortality are partly the result of differences in unmeasured risk factors, a change in transfer policy might not reduce mortality for babies of gestations of 28 weeks or less who are born in units outside the regional referral centre but it would increase the mortality rate for admissions to the referral unit as they take in higher risk babies. It might nevertheless wrongly be seen as a successful policy as mortality for admissions to the secondary level intensive care units would almost certainly be reduced as the case mix changed.

Another way of analysing the data is to look at the outcomes for defined cohorts of births related to access to different neonatal services, rather than at the mortality of admissions to different neonatal units.[7–9] This has added importance when the effect of prenatal and delivery room care on subsequent outcome of very preterm births is also recognised.[10 11] It is not enough to measure the outcome for babies of such low gestational age only in terms of mortality. Field *et al* plan to look at long term morbidity in the babies included in the Trent Neonatal Survey, and this will provide essential additional information for service planners who are trying to predict demands on families and health and social services.

Although it may be the case that care in a regional referral unit can improve the chance of survival for babies of gestations of 28 weeks or less, the problem still remains for those providing the service of how to ensure that all the babies have access to appropriate services, especially in rural areas with dispersed populations.

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The incidence of renal calcification in preterm infants

Andrew Short, Richard W I Cooke

Abstract

A total of 79 infants born at less than 32 weeks' gestation were studied with serial renal ultrasound scans to assess the incidence of nephrocalcinosis. Twenty one infants developed renal calcification giving an overall incidence of 26·6% in the study group. Affected infants were significantly smaller (mean (SD) birth weight 940 (323) g) and significantly less mature (mean (SD) gestation 26·9 (1·9) weeks). In 17 patients the calcification was represented by hyperechogenic renal pyramids alone, and in four patients renal calculi were demonstrated. Factors associated with renal calcification included hypophosphataemia, hypercalcaemia, hypercreatininaemia, and prolonged oxygen requirement during the first month of life. Multivariate analysis showed that the strongest clinical indicator of calcification was duration of oxygen treatment. Infants who still required oxygen treatment at 28 days had a 62% chance of developing renal calcification.

The tendency for calcium salts to deposit in the human renal tract has plagued mankind and provided employment for lithotomists for over 2000 years. Improved survival among preterm infants has resulted in a greater recognition of the complications of their medical management, which includes a risk of renal calcium deposition. The first reports of renal calcification appeared in 1982,[1] and subsequent reports continued to link it with hypercalciuria and frusemide administration.[2 3] Improvements in diagnostic ultrasound resulted in the increased recognition of this problem, and in 1988 Jacinto *et al* reported an incidence of 64% in infants below 1500 g birth weight.[4]

This report was the first to describe the occurrence of renal calcification in the absence of frusemide treatment. Despite the suggestion that two out of every three infants below 1500 g birth weight are likely to be affected, reports of renal calcification continue to be sporadic. Only three cases have been described in Britain, all of whom have been treated with frusemide.[5]

Factors that may contribute towards renal calcification include renal insufficiency, parenteral feeding, prolonged immobility, and bone demineralisation, all of which are commonly encountered in the sick preterm infant.

In view of the conflicting reports of the incidence of calcification in the face of known risk factors this study was designed to determine the incidence of and possible contributary factors towards renal calcification in preterm infants.

Patients and methods

All infants born before 32 completed weeks' gestation and admitted to our neonatal intensive care unit within 24 hours of birth were eligible for the study. Infants born elsewhere and transferred after 24 hours of age were excluded, as were those who were discharged or died before 7 days of age. Recruitment occurred only after the first week of life. The study protocol was approved by the local ethics committee.

Clinical data was recorded for the duration of each infant's admission. This included diagnosis, gestation, birth weight, duration of ventilation and oxygen treatment, aminoglycoside, steroid, and diuretic treatment, and prescribed and actual intakes of enteral and parenteral feeds.

Weekly intakes of calcium and phosphate were calculated from prescribed supplements if parenterally fed and using published concentrations of calcium and phosphate if milk fed. Human expressed breast milk was assumed to contain 8·75 mmol/l of calcium and 4·85 mmol/l of phosphate.[6]

Blood specimens were collected at least daily during periods of intensive care, and no less than weekly as the patients improved, to assess calcium, phosphate, and creatinine concentrations. Beyond 28 days of age serum alkaline phosphatase activity was measured once a week. Apart from creatinine, all biochemical analyses were performed using a Technicon autoanalyser in a clinical laboratory with staff experienced in handling neonatal specimens. Serum and urine creatinine estimation was by the Jaffé reaction.

After 7 days of age random urine specimens were collected at weekly intervals to measure calcium, phosphate, and creatinine concentrations. Calcium to creatinine ratios were calculated and tubular reabsorption of phosphate was determined using serum biochemical results from specimens obtained the same morning. Urine specimens were generally collected into a urine collecting bag but if this proved impractical then specimens were extracted from soaked napkins as described by Roberts and Lucas.[7] Over 80% of specimens were collected into urine bags, or extracted immediately from the napkin, with the remaining specimens divided equally between the two groups.

Renal ultrasound scans were performed employing initially an ATL scanner with 5 MHz probe, substituted with an Ultramark IV scanner and 10 MHz probe shortly after commencing the study. Scans were repeated on a weekly basis until discharge and hard copy prints were obtained and assessed by one of us (AS) for presence of calcification. Strict criteria

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Table 1 Infants with renal calcifications

Case No	*Sex*	*Gestation (weeks)*	*Weight (g)*	*Frusemide given*	*Age at diagnosis (days)*	*Site of calcification*	*Outcome*
1	F	26	986	Yes	41	R+L	Alive
2	F	24	612	No	37	L	Died
3	F	25	718	Yes	66	R+L	Alive
4	M	28	820	Yes	82	R+L	Died
5	M	26	1132	No	53	R+L	Alive
6	F	26	726	Yes	55	R+L	Alive
7	F	27	1192	Yes	36	L*	Alive
8	M	24	668	Yes	66	R+L	Alive
9	M	25	826	No	37	R+L	Alive
10	F	29	620	Yes	34	R+L	Alive
11	F	30	1856	Yes	55	R+L	Alive
12	F	24	760	Yes	32	R+L	Alive
13	F	28	1300	Yes	46	R+L	Alive
14	M	28	1178	No	43	R	Alive
15	F	29	1400	Yes	35	R+L	Alive
16	M	27	758	Yes	41	R+L	Died
17	F	27	850	No	47	R+L	Alive
18	F	27	812	Yes	47	R+L	Alive
19	M	26	1220	Yes	37	R+L	Died†
20	M	31	580	Yes	27	R+L	Alive
21	F	27	726	No	53	R+L	Died

*Patient had solitary kidney.
†Patient died three weeks after discharge.
R, right; L, left.

Table 2 Mean (SD) duration of respiratory illness

Variable	*Calcification (n=21)*	*Normal (n=58)*	*p Value*
Ventilation (days)	41 (25)	8 (12)	<0·001
Oxygen (days)	79 (31)	18 (20)	<0·001
Admission (days)	85 (30)	33 (17)	<0·001

were employed in making a diagnosis of renal calcification.[8] There had to be areas of hyperechogenicity visible in either the renal pyramids or renal pelvis on at least two consecutive scans, and even highly suspicious echoes were ignored unless accompanying acoustic shadowing was seen.

Statistical analysis was performed using Student's *t* test for normally distributed data and the Mann-Whitney U test for skewed data. Multivariate analysis was performed by computer employing the SPSSx statistical program.[9] Results are given throughout as mean (SD) unless otherwise stated.

Results

Over a 10 month period in 1989, 83 infants born at less than 32 weeks' gestation were admitted and survived beyond the first seven days of life. Of these patients four died or were discharged before the first renal ultrasound scan and are thus excluded from further analysis. Twenty one of the 79 remaining infants developed renal calcification giving an overall incidence of 26·6%. Renal calcification was bilateral in 18 cases and unilateral in three, one of whom had a solitary kidney. Calcification was detected at a mean age of 47 (14) days and affected boys and girls equally. Among the unaffected group four patients died while still at risk of developing renal calcification. There were four deaths in the affected group, and one late death after discharge from hospital.

Infants in whom calcification developed showed significant differences in birth weight (mean 940 (323) g compared with 1212 (362) g, p<0·002) and gestation (mean 26·9 (1·9) weeks compared with 28·8 (2·1) weeks, p<0·001). Details of affected patients are given in table 1.

Altogether 15 (71%) of the infants who developed calcification were prescribed regular frusemide treatment, compared with only 10 (17%) of the unaffected infants (p=0·001). The mean total dosage given was considerably higher in the group with calcification (138·5 (152) mg) than in the unaffected infants (21·8 (10·8) mg), although two patients prescribed frusemide had developed calcification before starting treatment. The mean total dose of frusemide prescribed before calcification was first detected was only 22·8 (23·2) mg.

All of the affected infants were ventilated for hyaline membrane disease, compared with 79% of the normal infants. Duration of ventilation and subsequent oxygen treatment were significantly longer in the affected group, all of whom went on to develop bronchopulmonary dysplasia (table 2).

Serum urea and creatinine concentrations were both significantly greater in the affected patients indicating a greater degree of renal insufficiency. Despite the very high values in some cases no patient required dialysis and by 4 weeks of age there was no difference between the two groups (fig 1).

There was no significant difference in either calcium:creatinine ratio (4·4 (4·1) compared with 4·0 (2·9), p=0·47) or phosphate:creatinine ratio (1·5 (1·8) compared with 1·3 (1·7), p=0·33) as measured on a molar:molar basis on specimens collected at 7 days of age. From 2 weeks of age, however, infants who subsequently developed renal calcification had significantly higher urinary calcium excretion. The difference was significant until week 6 after which small numbers of normal patients affected the statistical analysis (fig 2).

To ensure that the higher calcium:creatinine ratios in the affected group did not simply reflect diminished renal function with poor urinary concentration, mean values for urinary calcium and creatinine concentrations were also calculated for the first month of life. These showed both signficantly higher urine calcium

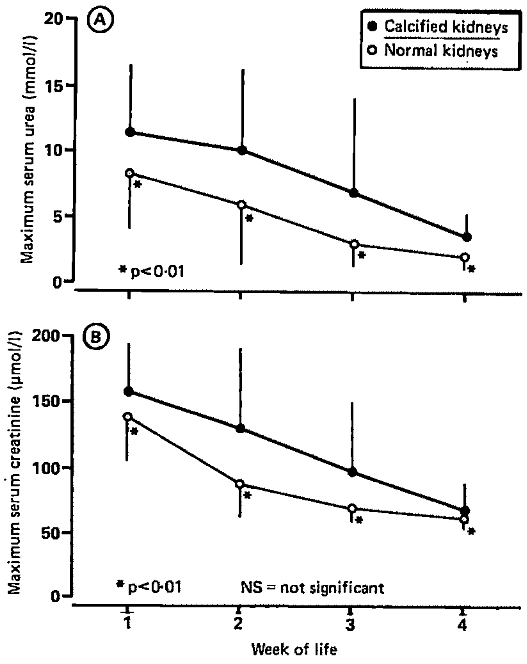

Figure 1 Mean maximum recorded serum urea (A) and creatinine (B) during the first four weeks of life for infants with normal concentrations and calcified kidneys, plotted to show mean (SD); NS=not significant.

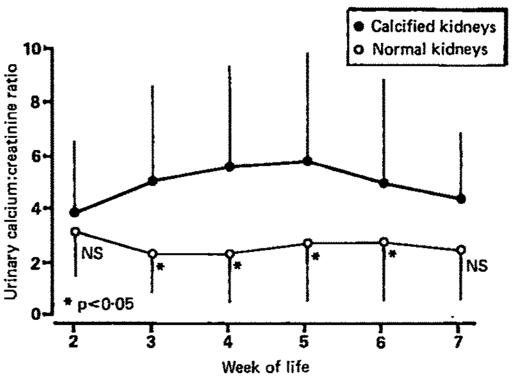

Figure 2 Mean calcium:creatinine ratio (mmol:mmol) in urine specimens collected during the first seven weeks of life for infants with normal and calcified kidneys, showing mean (SD); NS=not significant.

concentrations (3·12 (1·9) mmol/l compared with 2·27 (1·8) mmol/l, p<0·01) and significantly lower urine creatinine concentrations (810 (381) μmol/l compared with 1016 (502) μmol/l, p<0·01), both of which would contributed to the higher calcium:creatinine ratios.

Intakes of calcium, phosphate, and fluids were recorded for all patients during the first four weeks of life. The prescribed calcium intake was significantly less in the group with nephrocalcinosis for each of the first four weeks, though a difference in phosphate intake became apparent only after the first week. However, all of the parenterally prescribed calcium would enter the circulation, though only around 33% of calcium administered orally as preterm formula would be absorbed.[10] Therefore estimation of the actual calcium intake for the two groups showed no difference during the first month of life. Fluid intake was significantly lower in the group with nephrocalcinosis during the second and third weeks of life only (table 3).

The affected patients were more reliant on parenteral feeding as a source of fluid intake, with a delay in institution of milk feeds. The mean age at introduction of milk feeds was 11 (9) days in the unaffected patients but 30 (12) days in those who developed calcification (p<0·001).

The maximum recorded serum calcium and minimum recorded serum phosphate both showed significant differences between the two groups, although the minimum recorded calcium was not different (fig 3). Alkaline phosphatase activity, an indicator of osteopenia of prematurity, was consistently higher in the group with nephrocalcinosis. Mean maximum alkaline phosphatase activity in the nephrocalcinosis group was 1670 (770) IU/l compared with 890 (430) IU/l for the unaffected group (p<0·001).

Figures 4 and 5 show typical ultrasound appearances of hyperechogenic renal pyramids and a renal calculus. Both were detected using the Ultramark 4 scanner and persisted for several months, and were still present on discharge from the neonatal unit.

Table 3 Mean (SD) mineral and fluid intakes kg/day

Intake	*Week 1*	*Week 2*	*Week 3*	*Week 4*
Prescribed calcium (mmol)				
Nephrocalcinosis	0·90 (0·27)	0·94 (0·28)	0·94 (0·46)	1·18 (0·56)
Normal	1·08 (0·35)	1·57 (0·65)	1·89 (0·82)	2·06 (0·86)
	p=0·01	p<0·01	p<0·01	p<0·01
Estimated calcium (mmol)				
Nephrocalcinosis	0·89 (0·26)	0·91 (0·24)	0·83 (0·09)	0·86 (0·20)
Normal	0·87 (0·20)	0·87 (0·24)	0·88 (0·18)	0·89 (0·18)
	NS	NS	NS	NS
Phosphate (mmol)				
Nephrocalcinosis	0·55 (0·21)	0·67 (0·25)	0·74 (0·33)	0·91 (0·34)
Normal	0·61 (0·23)	0·98 (0·42)	1·16 (0·57)	1·28 (0·60)
	NS	p<0·01	p<0·01	p<0·05
Fluid (ml)				
Nephrocalcinosis	134 (35)	141 (34)	145 (22)	147 (19)
Normal	137 (25)	157 (21)	154 (15)	153 (23)
	NS*	p<0·01*	p<0·05*	NS*

Statistical analysis peformed using Mann-Whitney U test, except those marked* where Student's *t* test used; NS=not significant.
†Estimated calcium intake equals all prescribed parenteral calcium plus 33% prescribed calcium in oral feeds.

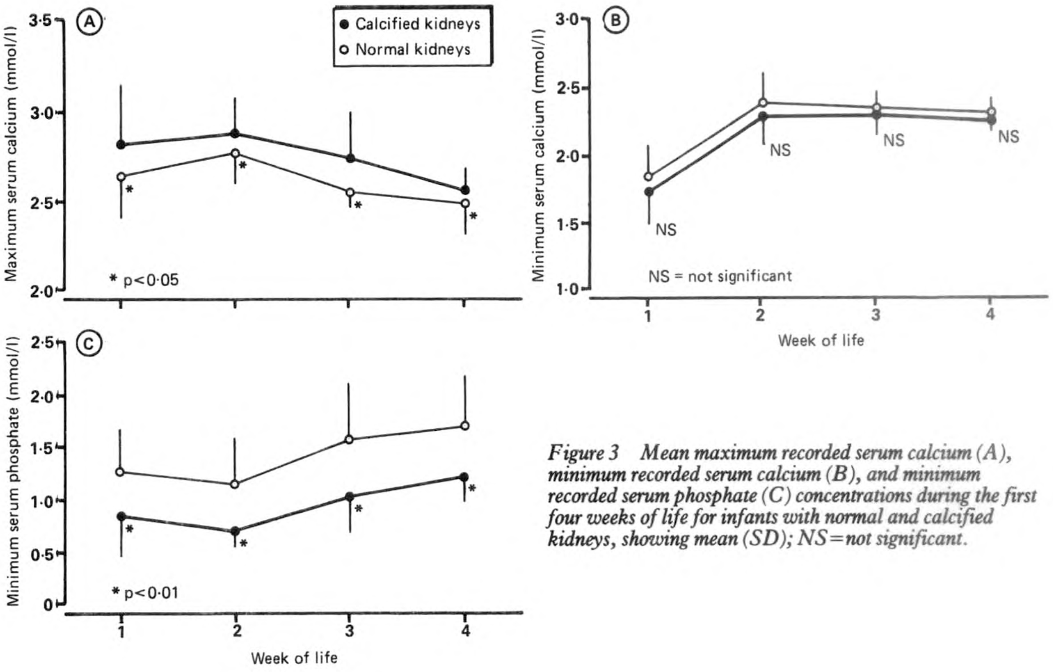

Figure 3 Mean maximum recorded serum calcium (A), minimum recorded serum calcium (B), and minimum recorded serum phosphate (C) concentrations during the first four weeks of life for infants with normal and calcified kidneys, showing mean (SD); NS=not significant.

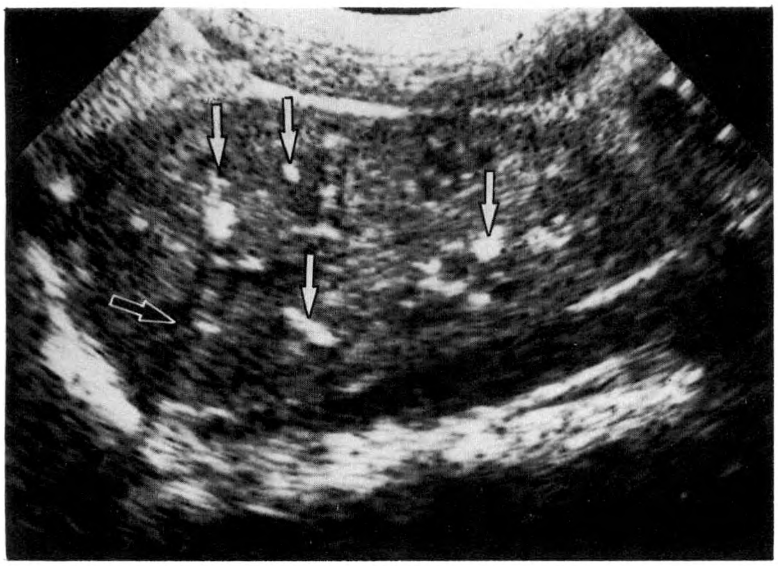

Figure 4 Ultrasound scan of a neonatal kidney demonstrating hyperechogenic renal pyramids (white arrows) with accompanying acoustic shadowing (black arrow). This patient was not treated with frusemide.

Discriminant analysis was performed using SPSSx statistical package. The presence of nephrocalcinosis was the dependent variable and serum calcium, phosphate, and creatinine concentrations, gestation, frusemide and oxygen treatment, age at introduction of milk feeds, and duration of admission acted as independent variables. The most significant predictor of calcification was duration of oxygen treatment with a residual variance of just 0·38. Addition of the three next variables (milk feeds, admission, and serum phosphate) decreased this only slightly to 0·31.

Computation of partial correlation coefficients showed that the association between calcification and oxygen treatment remained highly significant (coefficient 0·6, $p<0·001$) even after controlling for gestation and frusemide treatment.

Discussion

The original reports of renal calcification in preterm infants were often coincidental findings on routine chest or abdominal radiographs and as such probably reflected a more severe form. Prospective studies and improvements in diagnostic ultrasound have allowed earlier detection in larger numbers. Different diagnostic criteria are probably responsible for the even higher incidence reported by Jacinto *et al*,[4] and would also account for the appreciable difference in reported mortality which varies between 0 to 70%.

All studies seem to confirm that it is the smaller, more immature infant who is susceptible to calcification; the mean gestation of our patients corresponds well to those reported by both Ezzedeen *et al*[3] and Gilsanz *et al*.[2] Boys and girls appear to be equally at risk, the higher number of girls in our series simply reflecting the increased proportion of girls in the study group (13 out of 21 compared with 32 out of 58, $p=0·25$).

The mean age at diagnosis was 47 (14) days with a range from 32 to 82 days. Most cases (n= 15) were detected in the fifth, sixth, or seventh week of life. Where our findings differ significantly is in the apparent effect of frusemide. Although affected patients are more likely to have received frusemide, there is no difference in the mean total dose given before detection of calcification and the mean total dose given to unaffected patients. This appears to suggest that frusemide is prescribed for infants who are already at risk of renal calcification because of other factors, and the suggestion that frusemide

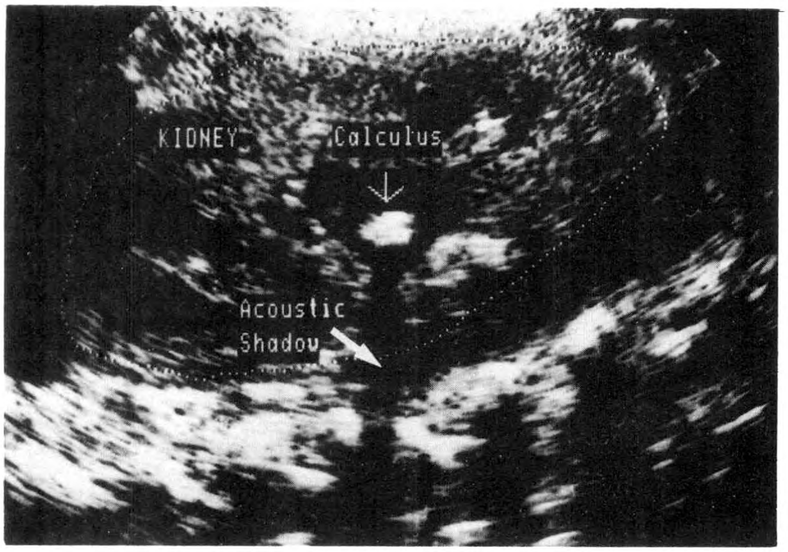

Figure 5 Ultrasound scan demonstrating a renal calculus in the left renal pelvis with accompanying acoustic shadowing. This patient was treated with regular frusemide from 11 days of age.

induced hypercalciuria is the predominant factor in aetiology is an oversimplication of the complex interaction of risk factors in these infants.

Assessment of urinary calcium excretion suggests that all preterm infants begin life with relative hypercalciuria. Although this tends to improve in the unaffected group, the tendency in the group with calcification is for a progressive increase in renal calcium excretion. This hypercalciuria is regularly detected before the introduction of frusemide, after which individual patients may show either increases or decreases in calciuria. The measurement of calcium:creatinine ratios on random specimens of urine has previously been validated,[11] but there is no doubt that 24 hour urine collections give a more accurate indication of calcium excretion. The extraction of specimens from wet napkins may also lead to errors in estimation of urinary calcium, although prompt collection of urine once voided will minimise this problem.[7] Nevertheless this potential source of error may account for the relatively high values obtained in our patients compared with the figures previously reported by Karlen *et al*.[10]

A further problem related to the use of calcium:creatinine ratios is that the figures obtained by Karlen *et al* represent healthy infants with normal renal function, and hence a normal ability to concentrate urinary creatinine. Due to renal impairment the sick preterm infants in our study showed diminished urinary creatinine concentration, more noticeably in the group with nephrocalcinosis. Although to interpret a high calcium:creatinine ratio in such circumstances as indicative of hypercalciuria may be wrong, it would appear that both higher calcium excretion and lower creatinine excretion contribute to the increased ratios.

We did not assess urinary stone inhibitors in this study. There is, however, some evidence suggesting that urinary citrate tends to fall with rises in urinary calcium, and urinary magnesium is also lower in infants with nephrocalcinosis who are receiving frusemide.[11] The role of urinary uric acid excretion in the aetiology of renal calcium deposition in preterm infants remains unclear.

In order for urinary crystallisation and stone formation to occur the urine must be supersaturated with calcium. Given a constant rate of calcium excretion urinary calcium saturation will be greater at times of low urinary production. We have not measured urine output in our patients, although it would seem likely that the raised serum creatinine concentrations in affected infants may have been accompanied by varying degrees of oliguria. Ezzedeen and colleagues identified oliguria (<1·5 ml/kg/hour) as a risk factor for renal calcification found in 59% of their cases, although no data are provided for suitably matched controls.[3] If facilities are available for accurate monitoring of urine output, particularly during the initial period of intensive care, then a documented period of oliguria may well be a further indicator of infants at risk of nephrocalcinosis.

Similarly acidosis has been suggested as a further risk factor for nephrocalcinosis,[3] in view of the resulting increase in calcium excretion. However both metabolic and respiratory acidosis occur so commonly in sick preterm infants, whom we have already identified as the group at risk of renal calcification, that the presence of a low pH is unlikely to increase significantly the ability to identify potentially affected infants.

Hypercalciuria is a recognised consequence of hypophosphataemia, which we have demonstrated in our patients throughout the first month of life. There has been considerable interest in the role of phosphate intake in the aetiology of osteopenia of prematurity,[12 13] and it would appear that it is similarly implicated in renal calcium deposition. Exact phosphate requirements in sick preterm infants are difficult to establish, but recent reports suggest 1·4 mmol/kg/day may be the optimal figure.[14 15] The currently used parenteral feeding regime on our unit provides only half this amount, and may be partly responsible for the high incidence of nephrocalcinosis. Ensuring adequate phosphate intake would not only reduce hypercalciuria, it may also erradicate osteopenia of prematurity.[16] The solubility of phosphate in parenteral feeding solutions causes problems in administration, however, and caution is needed when prescribing phosphate supplements in the presence of appreciable hypercalciuria. Too much phosphate may result in the anticipated calcium deposition occurring renally rather than skeletally.[17]

The high alkaline phosphatase activity that we found in our patients is not surprising given the intricate association between the skeleton and renal tract in calcium and phosphate homoeostasis. The role of vitamin D in this association is difficult to establish. Vitamin D supplements (400 units/day) were given orally to infants once enteral feeds were established, and hence they were introduced at a significantly earlier age in unaffected patients (22 (15) days compared with 52 (23) days, p<0·001). Infants on parenteral feeds were prescribed a mean of 160 units per day of vitamin D intravenously. If vitamin D contributed towards the hypercalciuria one would expect to find affected infants receiving more rather than less vitamin D. During the first weeks of life in sick preterm infants the vitamin D requirement is not clear, however, and the low doses administered in our patients still exceed (on a unit/kg basis) the apparent requirement of 30 units/kg recommended by Koo.[18]

Relative immobility is common to all infants in the neonatal period, but by 8 weeks of age the bone mineral content of term infants begins to rise.[19] For a sick preterm infant ventilated and in an incubator it may be several weeks before his movements approximate to those of a term infant, and this relative immobility may well contribute towards the hypercalciuria. Equally the prolonged periods of parenteral feeding may be responsible. Intravenously administered calcium and parenteral feeding have been associated with renal stone formation in older patients,[20] and there are theoretical reasons for concern over oxalate precursors in parenteral feeds.[21] Though enteral feeds in sick infants are not without risk, the greater intake of phosphate that they allow is just one reason why their early introduction should be considered.

We have shown that the duration of oxygen treatment, and hence the presence of chronic lung disease, acts as a very useful indicator of the risk of renal calcification. Many different facets of neonatal management may be responsible for this increased risk, including the use of frusemide. Rare disorders such as primary hyperparathyroidism and a variant of Bartter's syndrome should be considered,[22] particularly in the absence of chronic lung disease, but most sick, preterm infants have sufficient calciuric stimuli that the addition of frusemide is not necessary to induce renal calcification.

Long term follow up of affected patients is needed to assess the significance of this calcification. Complications of renal calculi, such as infection, obstruction, and haematuria are well recognised. There is understandable concern about long term renal function in the presence of nephrocalcinosis, but in the small number reported by Ezzedeen *et al* other complicating factors make interpretation of his findings difficult.[3] Four of our affected patients had acute tubular necrosis with oliguric renal failure, the effects of which must also be considered in subsequent follow up.

While awaiting data on the sequelae of nephrocalcinosis in preterm infants, efforts should be directed towards reducing urinary calcium saturation. In addition further work is required to establish the role of urinary inhibitors of stone formation. Controlled trials are needed to compare the effects of different diuretic treatments and different phosphate intakes on the incidence of nephrocalcinosis.

We thank the nursing staff of the neonatal intensive care unit at Liverpool Maternity Hospital; Dr T McKendrick for helpful advise and criticism; and the Alder Hey Children's Kidney Fund for financial support.

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effect of gestation: firstly a linear regression analysis was done to look for an association between gestation and birthweight ratio; secondly, multiple regression analysis was used when adjustment for confounding factors was required.

Results

GROUP 1

The birthweight ratio data for all babies in group 1 (that is, all babies of less than 31 weeks' gestation born between January 1985 and December 1989) conformed closely to a Gaussian distribution (χ^2 test, p=0·09), with no apparent skewness. The sample mean (SEM) was 1·0097 (0·0095) (fig 1).

The mean (SEM) birthweight ratio of the 57 babies in group 1 who died was 1·026 (0·0083). This was not significantly different from that of the survivors (Student's *t* test, p=0·466). There was, however, a significant difference between the mean gestational ages of the two groups, 27·3 weeks and 28·9 weeks, respectively (p= <0·001).

In addition to adjusting for gestation with multiple regression, we checked to see if there was any significant correlation between birthweight ratio and gestation that would have prevented us from detecting an influence of birthweight ratio independent of gestation; there was none (=−0·077, p=0·13).

Birthweight ratio was divided into five categories and these were regressed as discrete variables against whether each subject died in the neonatal or postneonatal period; adjustment was made for gestational age. There was no significant association (p=0·89) (table 1). The birthweight ratio was also regressed as a continuous variable against whether each subject died in the neonatal or postneonatal period, adjusting for gestation by multiple regression analysis. No significant association was found (p=0·9).

Linear regression analysis was used to examine the relationship between the birthweight ratio of the survivors of the neonatal period and the duration of mechanical ventilation. No significant association was found (r= −0·0097) (fig 2). Multiple regression was then used to make adjustment for gestation and once again no significant association was found (p= 0·211).

The survivors were then divided into five discrete birthweight ratio classes (<0·8, 0·8–<0·09, 0·9–<1·0, 1·0–<1·1, ≥1·1) and these were related to the duration of ventilation divided into four classes (during the first 24 hours and greater than seven, 14, and 28 days). There was no significant association between birthweight ratio category and the duration of mechanical ventilation (χ^2 test, p=0·83). Multiple regression analysis was used to relate birthweight ratio as a discrete and a continuous variable to duration of ventilation among the survivors; adjusting for gestation no association was found (p=0·18). Table 2 shows the percentage of babies in each birthweight ratio category

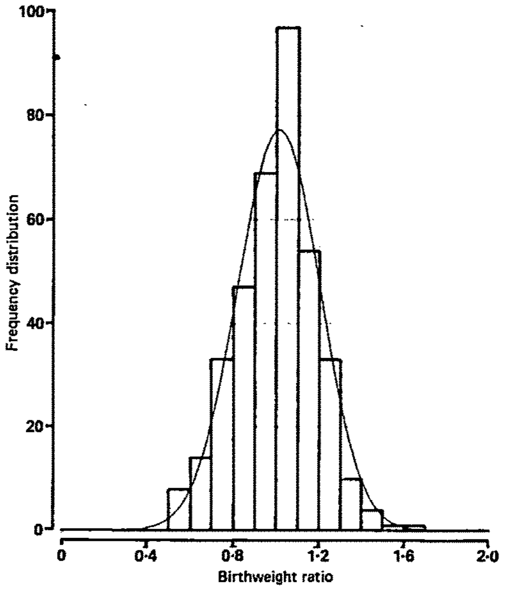

Figure 1 Frequency distribution of birthweight ratios for babies in group 1.

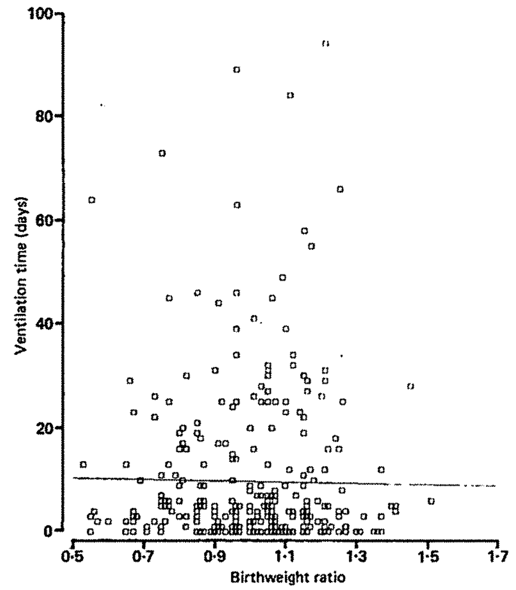

Figure 2 Regression line of duration of ventilatory support in days and birthweight ratio.

Table 1 Association between birthweight ratio and number of babies that died adjusted for gestational age

	Birthweight ratio				
	<0·8 (n=49)	*0·8–<0·9 (n=42)*	*0·9–<1·0 (n=64)*	*1·0–<1·1 (n=102)*	*≥1·1 (n=115)*
Gestation:					
Mean gestational age	29·1	28·5	29	28·6	28·4
No (%) that died ≤28 days old	5 (8)	8 (14)	7 (10)	11 (11)	20 (18)
No (%) that died >28 days old	1 (1·7)	0	2 (3)	0	3 (2)

p=0·9 for birthweight ratio (as a continuous variable) regressed against whether each subject died in the postneonatal period (adjusting for gestation).

Table 2 Association between birthweight ratio and need for mechanical ventilation

	Birthweight ratio				
	<0·8 (n=44)	*0·8–<0·9 (n=34)*	*0·9–<1·0 (n=57)*	*1·0–<1·1 (n=91)*	*≥1·1 (n=95)*
No (%) ventilated during first 24 hours	37 (84)	28 (82)	38 (67)	66 (73)	73 (77)*
No (%) ventilated for >7 days	14 (32)	15 (44)	18 (32)	20 (22)	33 (35)**
No (%) ventilated for >14 days	8 (18)	10 (29)	15 (26)	15 (17)	24 (25)***
No (%) ventilated for >28 days	4 (9)	2 (6)	8 (14)	6 (7)	12 (13)****

*p=0·18, **p=0·84, ***p=0·58, ****p=0·14, for birthweight ratio (as a continuous variable) regressed against the need for ventilation in the first 24 hours and greater than 7, 14, 28 days (adjusting for gestation).

needing mechanical ventilation during the first 24 hours and for greater than seven, 14, and 28 days. There was no significant association between birthweight ratio groups and the need for mechanical ventilation in any of the categories after adjusting for gestation (p=0·18, p=0·84, p=0·58, and p=0·14, respectively).

GROUP 2

The birthweight ratios of the children with confirmed cerebral palsy also fitted a Gaussian distribution (mean (SEM) 1·057 (0·023)). This mean birthweight ratio was slightly higher than that of the group 1 babies, but the difference was not significant (p=0·061). There was, however, a significant difference in gestational age between the two groups, those with cerebral palsy having a lower mean gestational age (28·14 weeks) than the group 1 mean (28·93 weeks, p=0·003).

There was no difference in birthweight ratio among the various cerebral palsy groups: diplegia (n=45), quadriplegia (n=9), hemiplegia (n=6), and athetoid (n=2).

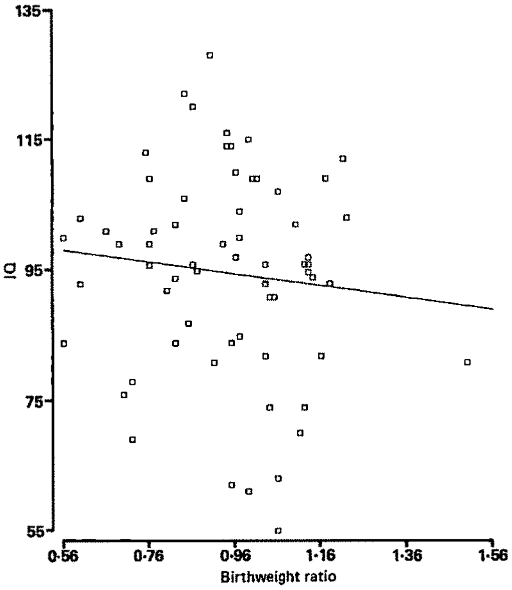

Figure 3 Regression line of IQ and birthweight ratio.

GROUP 3

Data about the infants in the very low birthweight follow up study were analysed in a similar way. The mean (SEM) birthweight ratio for this group was 0·94 (0·021). Nine babies in the group had cerebral palsy (diplegia (n=7), quadriplegia (n=1), and hemiplegia (n=1)). The mean (SD) birthweight ratio of the babies with cerebral palsy was 0·987 (0·024). This was not significantly different from the population mean (p=0·52). The mean gestational age was also not significantly different (28·7 weeks for babies without cerebral palsy compared with 27·89 weeks for those with cerebral palsy, p=0·16).

The IQs of the very low birthweight group were normally distributed around a mean of 94·8. There was no significant correlation between either birthweight ratio and IQ (fig 3) or between gestation and IQ (r=−0·17 and 0·2, respectively). The VQs for the group were normaly distributed about a mean of 97·1, and there were no significant correlations between birthweight ratio or gestational age or VQ (r=−0·2 and 0·2). Multiple regression analysis was then used to analyse the association between birthweight ratio as a discrete variable and IQ and VQ, adjusting for gestational age. No significant association was found (p=0·74 and p=0·58, respectively) (table 3).

Morley *et al* found an association between birthweight ratio and body weight, body length, and head circumference at 18 months when adjustment was made for gestational age. We have no data to verify these findings.

Discussion

The birthweight ratio is a concept that has instant appeal. It is much easier to handle than centile charts and overcomes the previous arbitrary categorisation of babies according to centile lines. Its use should allow more sensitive analysis of outcome depending on intrauterine

Table 3 Association between birthweight ratio, IQ, and VQ

	Birthweight ratio				
	<0·8 (n=14)	*0·8–<0·9 (n=10)*	*0·9–<1·0 (n=15)*	*1·0–<1·1 (n=11)*	*≥1·1 (n=14)*
Mean (SEM) IQ	94·6 (3·5)	99·7 (4·1)	98 (5·1)	92·5 (4·4)	89 (4·5)
Mean (SEM) VQ	98·2 (3·8)	101·7 (4·4)	99·13 (4·6)	97 (4·3)	91·2 (3·7)

growth. The Cambridge data seem to confirm this hope in relation to the severity of respiratory disease, the postneonatal mortality rate, long term growth, and possibly language development. Its potential usefulness is so great that we felt it should be tested on another group.

In the calculation of birthweight ratios for babies born in Leeds we made use of the median birthweight data produced by Lucas *et al* because we do not yet have sufficient data of our own.[1] The close proximity of our mean birthweight ratio to unity and the normal distribution about the mean suggests that these data are suitable. We did not see the slight negative skewness that was seen in the distribution of the Cambridge data, but numbers in both groups are too small to make much of this difference. It is unlikely that we studied a significantly lower proportion of babies delivered electively for suspected intrauterine growth failure.

The mean birthweight ratio of our group of babies weighing less than 1500 g (group 3) was, not surprisingly, significantly lower than that for our general population of babies born at less than 31 weeks' gestation because the weight limit will have exluded some babies with higher birthweight ratios.

We were unable to show any association between the birthweight ratio and either the need for, or the duration of, ventilatory support (fig 2, table 2). This was a surprise because we had expected to find that babies whose birth weights were lower than expected for gestational age would have less severe respiratory distress syndromes and less chronic lung disease than those who were better grown. Unlike the Cambridge study, which may have excluded some babies dying during the first day or two of life, our data on mortality are complete.

Morley *et al* found a significant association between birthweight ratio category and postneonatal mortality, suggesting that babies with a low birthweight ratio had a higher postneonatal mortality rate. We found no statistical association between birthweight ratio and mortality rate either during or after the neonatal period. An interesting difference between our group and that described by Morley *et al* is the much lower postneonatal mortality rate among Leeds babies (1·87% compared with 6·77%); it was so low that we are unable to comment on any relationship with birthweight ratio. The overall mortality rates for the two cohorts are, however, similar (16·5% in Cambridge and 15·5% in Leeds). The observed shift in age at death may be explained either by an intrinsic difference between the two populations or by a difference in clinical practice. There is insufficient information to take this any further.

We have no ready explanation for the many differences between our findings and those of Morley *et al*, or conventional teaching, although perhaps the current use of steroids, both prenatally and postnatally, may have altered the pattern of respiratory distress compared with older studies.

We would have expected to find an association between birthweight ratio and developmental outcome, because adverse prenatal factors affect both somatic growth and the growth and development of the central nervous system. The Cambridge study was unable to show such an effect, except for slightly better language scores at 18 months in infants with the highest birthweight ratios. Despite having detailed neurological and psychometric developmental assessments at the age of 5 years we were also unable to find any association between birthweight ratio and either neurological or intellectual outcome. We can offer no clear explanation for the lack of relationship between birthweight ratio and developmental outcome in our study and of Morley *et al*, except that both groups may have been too small to show it reliably. In the case of older studies it may be that, because estimates of gestation were less reliable than they are now, the effects of gestation were more difficult to disentangle from the effects of growth alone. In addition, the use of conventional centiles is already biased by the over-representation of growth retarded babies, and result in the selection of only the most extremely light for dates babies to compare with the rest of the population.

We are forced to conclude that for our babies the birthweight ratio is of no value in probabilistic calculations concerning the likely mortality, the duration of ventilator treatment, or the neurodevelopmental outcome among preterm babies of less than 31 weeks' gestation. We think that it is important for the question to be examined among a much larger number of infants from other centres.

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Iron supplementation, maternal packed cell volume, and fetal growth

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Abstract

Previous studies have found that there is a correlation between mothers' haemoglobin concentration or packed cell volume and infants' birth weight, and that iron supplementation increases mothers' haemoglobin concentration. The purpose of this study, using the data of a large randomised trial on iron prophylaxis during pregnancy, was to find out whether iron supplementation causes fetal growth to deteriorate. At their first antenatal visit, 2912 pregnant women were randomised into non-routine iron and routine iron supplementation. The mean length of gestation was shorter in the non-routine group. Birth weight did not differ between the groups, but due to longer gestations boys in the group receiving routine iron were taller than in the non-routine group. In both groups, whether studied by various values of packed cell volume or correlation coefficients, the lower the packed cell volume, the heavier and taller the infant and heavier the placenta. These negative correlations could be seen even with a packed cell volume measured early in preg-

haemoglobin and poor obstetric outcome are both related to low plasma volume.[10 12 20] Because of selection to iron treatment by haemoglobin concentration, this question can be answered only by studies using experimental designs. Using data of a large randomised trial comparing non-routine and routine iron prophylaxis during pregnancy, we describe the relation of fetal growth to iron supplementation and the mother's packed cell volume and blood pressure.

Subjects and methods

The study design, methods, and population have been reported in detail previously.[21] In brief, a multicentre trial comparing two policies of iron prophylaxis in pregnant women was carried out within routine health services. All mothers entering the 27 participating maternity centres were included in the study with the following exceptions: mothers with a serious chronic disease, a packed cell volume ≤0·32 or haemoglobin ≤110 g/l, the likelihood of moving from the area before the birth of the child, or

[redacted]

asked for routinely made measurements of packed cell volume or haemoglobin and blood pressure around the 12th, 20th, 28th, and 36th week. Equipment available in the centre determined whether packed cell volume (91% of the mothers) or haemoglobin concentration was used. Pack cell volume was measured for capillary blood by the centrifuge method. We changed haemoglobin concentrations into packed cell volume by a formula obtained from the local laboratory: packed cell volume=(haemoglobin+3·171)/3·488. Placental weight was also obtained from the form filled in by the midwife.

The *best estimate* of the length of gestation was drawn from the infant's hospital record, completed from the midwife's questionnaire for 15 infants whose records were not found, and rounded off to the nearest week. (Clinicians define gestation length by combining information from various sources, including ultrasound, history of last menstrual period, and clinical signs. The accuracy of measurements may vary from one infant to another, but we assume any inaccuracies to be similarly distributed in the two groups.) In addition, gestation length was calculated in days from the last menstrual period. Unless otherwise specified, the best estimate is used in analyses. Birth weight, birth length, and head circumference were determined from the infant's record. Infants whose weight fell below the 10th centile for that gestational age[19] were called small for their gestational age. Growth after birth was calculated by subtracting from each infant's weight in the postpartum check up her/his birth weight (g) and dividing by the age (in days).

To learn the prognostic value of the packed cell volume, mothers were classified by the result in the 12th week ($\leq$0·35, 0·36–0·38, 0·39–0·41, $\geq$42), and the 28th week ($\leq$0·32, 0·33–0·35, 0·36–0·38, $\geq$0·39); mothers with unknown values (n=59 and 76) were excluded from these analyses.

Pearson's correlation coefficient (r) and partial correlation coefficients standardised for other variables were calculated by the BMDP statistical package. Statistical significances were tested by χ^2 test (distributions), the test of two proportions (percentages), and *t* test (means).

Results

GESTATION LENGTH AND GROWTH BY IRON SUPPLEMENTATION

The mean length of gestation was somewhat shorter in the non-routine group, but was significant only among boys (table 1). In the non-routine group somewhat more girls were born in the 39th week (21·0% compared with 16·8%) and fewer in the 41st week or later (33·4% compared with 38·0%) than in the group receiving routine iron. Among boys there were more preterm births ($<$37 weeks) in the non-routine group (4·8% compared with 2·6%) and fewer births in the 41st week or later (34·9% compared with 39·8%). When gestation length was calculated from the last menstrual period, excluding women having gestation $\geq$46 weeks, the mean gestation length was 39·9 weeks in the non-routine group and 40·1 weeks in the group receiving routine iron ($p<0·05$). These differences were also found when only women with a spontaneous start of labour were studied.

The boys in the group receiving routine iron were, as a mean, 36 g heavier (not a significant difference) and 0·2 cm taller (table 1). This was due to longer gestation rather than quicker growth, however, and the mean birth weights in each gestation age were similar. Among girls, all indicators of growth (birth weight, length, head circumference, both means, distributions, and gestation specific values, and proportion of infants small for gestational age) were similar in the non-routine group and group receiving routine iron. Growth from birth to the postpartum examination was similar in the two groups.

In both groups boys were taller and heavier than girls, but that difference emerged only in the 38th week for height and in the 40th week for weight.

GESTATION LENGTH AND GROWTH BY PACKED CELL VOLUME

With gestation, the mothers' packed cell volume became lower in the non-routine group than in the group receiving routine iron (figure). In the non-routine group, the packed cell volume decreased until the 28th week. In the group receiving routine iron the decrease stopped by the 20th week. The higher the initial packed cell volume ratio, the greater the decrease in both groups.

We investigated the means and distributions of birth weight, birth length, and gestation length in the different groups of packed cell volume measurements in the 12th and 28th week. In the groups of high packed cell volume, mean birth weight and birth length were lower, and the proportion of infants weighing less than 2500 g was higher. Table 2 gives the results by the packed cell volume result in the 28th week. Similar results were obtained in the 12th week,

Table 1 Comparison between 1355 infants whose mothers received iron non-routinely and 1335 whose mothers received iron routinely. Values are expressed as mean (SD) except where otherwise stated

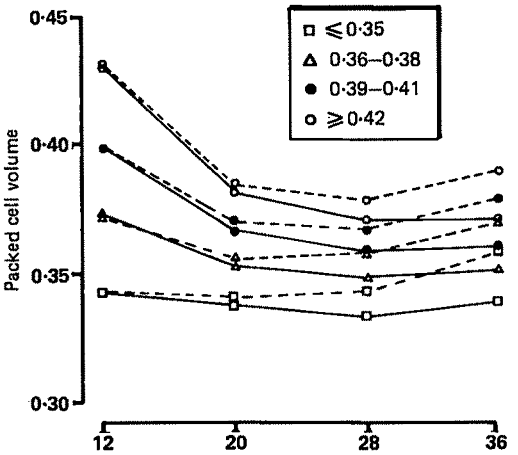
	Girls		*Boys*	
	Non-routine iron (n=670)	*Routine iron (n=689)*	*Non-routine iron (n=685)*	*Routine iron (n=646)*
Gestation (weeks)	39·7 (1·9)	39·8 (1·9)	39·7 (2·0)*	39·9 (1·8)*
Birth weight (g)	3511 (542)	3515 (544)	3622 (576)	3658 (568)
Length at birth (cm)	49·7 (2·5)	49·7 (2·4)	50·5 (2·5)*	50·7 (2·4)*
Infants small for gestational age (%)	6·3	6·7	5·7	4·2
Growth after birth (g/day)	27·9 (10·4)	27·3 (10·1)	31·4 (11·7)	32·2 (13·0)

*Boys whose mothers received iron non-routinely compared with boys whose mothers received iron routinely: $p<0·05$.

Table 2 Birth weight and gestational age by packed cell volume in mothers during 28th week

	Packed cell volume:non-routine iron (n=1319)				*Packed cell volume:routine iron (n=1299)*			
	≤0·32	*0·33–0·35*	*0·36–0·38*	*≥0·39*	*≤0·32*	*0·33–0·35*	*0·36–0·38*	*≥0·39*
No of mothers	162	462	513	182	(58)	395	586	260
Mean (SD) birth weight (g)	3690(531)	3581(532)*	3574(538)*	3421(643)**	3556(536)	3618(520)	3601(552)	3522(579)*
Birth weights <2500 g (%)	1·9	2·6	2·1	7·7*	(5·2)	1·3	2·4	5·0**
Infants who were small for gestational age (%)	5·6	5·0	5·8	9·3	(8·6)	4·3	4·9	6·9

*=p<0·05, and **=p<0·01 when compared with those with packed cell volume ≤0·32 in the group who received iron non-routinely, and when compared with those with packed cell volume 0·33–0·35 in the group who received iron routinely (because of the small number of women in this group with packed cell volume ≤0·32).



Changes in mean packed cell volume measured in the 12th week of gestation in mothers receiving iron non-routinely (solid line) and those receiving it routinely (broken line).

but the differences were not larger in the non-routine than in the group receiving routine iron as in the 28th week. The relation between packed cell volume in the 12th and 28th weeks and gestation length was weaker and not significant.

We also studied the relation between packed cell volume in the 12th, 20th, 28th, and 36th weeks and birth weight, birth length, head circumference, and gestation length by counting correlation coefficients. Weak negative correlations to weight and length could be seen in all packed cell volume measurements, but were usually strongest in the 36th week: the lower the packed cell volume the heavier and taller the infant. Correlations with head circumference were also negative, but weaker than those of weight or length. The negative correlation of the packed cell volume with gestation length was weaker than that with weight, and significant only in the iron group in the 36th week.

INTERVENING VARIABLES

To examine the relation between high packed cell volume and low birth weight we studied blood pressure and placental weight as possible intervening variables. Both groups were fairly similar to each other in blood pressure, proteinuria, and mothers' weight gain during pregnancy, and in placental weight. In both groups, high blood pressure, especially diastolic, correlated positively with the packed cell volume in the 36th week, negatively with gestation length, and weakly with birth weight (table 3) and birth length. Correlation coefficients with blood pressure in the 12th and 28th week tended in the same direction as those in the 36th week, but were usually smaller, with the exception of packed cell volume, with which the correlations were equally strong.

Table 3 Correlations between mothers' diastolic blood pressure in the 36th week and placental weight with packed cell volume, length of gestation, and birth weight

	Non-routine iron (n=1120–1206)	*Routine iron (n=1127–1181)*
Diastolic blood pressure:		
Packed cell volume, 36th week	0·20***	0·20***
Length of gestation	−0·17***	−0·16***
Birth weight	−0·11***	−0·09**
Placental weight:		
Packed cell volume, 36th week	−0·13***	−0·07*
Length of gestation	0·26***	0·28***
Birth weight	0·68***	0·68***

*=p<0·05, **=p<0·01, and ***=p<0·001.

Table 4 Raw and partial correlation coefficients (standardised for systolic and diastolic blood pressure) of the packed cell volume in the 36th week with gestation length, birth weight, and placental weight

	Non-routine iron (n=1153–1177)		*Routine iron (n=1154–1168)*	
	Raw	*Partial*	*Raw*	*Partial*
Gestation length	−0·04	−0·01	−0·09**	−0·07*
Birth weight	−0·13***	−0·11***	−0·12***	−0·10***
Placental weight	−0·13***	−0·13***	−0·07*	−0·07*

*=p<0·05, **=p<0·01, and ***=p<0·001.

Weight of placenta correlated positively with birth weight, birth length, and gestation length, and, especially in the non-routine group, negatively with the packed cell volume (table 3). On the other hand, there was no correlation between placental weight and systolic blood pressure (−0·01 in the 36th week, both groups combined) and only a weak correlation with diastolic blood pressure (−0·05 in the 36th week).

To abolish the association caused by joint correlations with blood pressure, partial correlation coefficients were calculated standardising for blood pressure. Standardisation only marginally changed correlation between packed cell volume and birth weight and placental weight (table 4). Similar changes after standardisation were observed for the measurements of packed cell volume in the 12th and 28th weeks.

Discussion

Mothers having a high packed cell volume had lighter infants and smaller placentas, and the negative correlation could be seen both with the packed cell volume in early and late gestation. Correlations with birth length, head circumference, and gestation length were weaker. The inverse association between a high packed cell volume in late pregnancy and poor infant growth has been documented previously,[9–11] but in this study it was found also for the packed cell volume measured in early pregnancy. In the study of Murphy *et al* the association was U shaped.[12]

Iron supplementation increased packed cell volume ratios, but it did not influence birth weight. High packed cell volume ratios relating to poor growth are thus probably caused by factors other than iron. Contrary to our hypotheses no clear sex specific differences in growth by iron supplementation emerged. Our results are contrary to previous controlled trials among pregnant women[22–25] and among rats,[26] which have consistently reported lower birth weight in the group receiving iron. However, all studies involved a small number of subjects, and among human beings these differences have not been significant.

As in the study of Murphy *et al* there was a positive correlation between a high packed cell volume and high blood pressure.[12] Standardising for blood pressure did not influence the correlations between packed cell volume and birth weight and packed cell volume and placental weight. Thus it seems that packed cell volume does not influence birth weight by blood pressure, but by some other mechanism such as small plasma volume and increased blood viscosity with impaired placental circulation.[12 27–29] Noteworthy is the fact that the negative correlation with birth weight could be seen even with packed cell volume measured early in pregnancy.

The prediction of poor growth by a high packed cell volume was clearer in the non-routine group. Apparently iron supplementation transferred several 'healthy women' to the group with a high value, and this diluted the association between the high value for packed cell volume and poor growth of the fetus. Even though routine iron supplementation does not seem to diminish growth, it may impede diagnosis of poor growth.

Gestation length was somewhat shorter in the non-routine group, especially among mothers with boys. The difference was mainly due to different distribution within 39–42 weeks; thus it is possible that iron postpones that start of labour at term. The mechanism remained unclear. It was not through packed cell volume, high blood pressure, or inductions. Nor is it likely to be due to varying calculations of gestation length, because it could be seen also with gestation length calculated from the last menstrual period.

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Comparison of triggering systems for neonatal patient triggered ventilation

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Abstract

The efficacy of two triggering systems was compared during neonatal patient triggered ventilation: the Graseby MR10 respiration monitor and airway pressure changes. Ten preterm infants were studied, median gestational age 33 weeks (range 28–35). Patient triggered ventilation was administered via the SLE ventilator at a series of inflation times (0·24, 0·3, and 0·4 seconds). Comparison was made between the trigger systems of the trigger delay, inflation volume delivered, and proportion of spontaneous respiratory efforts detected. The airway pressure trigger gave a superior performance: at the two lower inflation times the trigger delay was shorter and inflation volume delivered greater. At the longest inflation time a greater proportion of respiratory efforts were detected. We concude the airway pressure trigger should be used in preference to the respiration monitor as the triggering system of choice for neonatal patient triggered ventilation.

Patient triggered ventilation has now been available for neonatal use for about three years.[1] The commercially available system incorporates as a trigger system a Graseby MR10 respiration monitor. The Graseby capsule detects the infant's respiratory efforts by changes in abdominal expansion and is commonly used for the detection of central apnoea. The signal from this capsule can be used to trigger the manual breath control of the SLE ventilator. The ventilator so triggered delivers a single positive pressure inflation of magnitude and duration previously determined in conventional mode. Using this system one centre has demonstrated, in a small number of infants, improved gas exchange when compared with conventional ventilation.[1] They have also claimed that patient triggered ventilation is associated with a lower incidence of pneumothorax,[2] but only made comparison with historical controls. Although this triggering system is now commercially available, it remains in limited supply and no other centres have reported on the efficacy of this system.

We have also had experience of patient triggered ventilation and reported similar short term benefits—that is, improvements in blood gases.[3 4] These results, however, were obtained using a variety of other triggering mechanisms: changes in oesophageal pressure or airflow.[3 4] Oesophageal pressure changes provide an effective trigger system in the short term, but the sensitivity gradually declines with the build up of secretions and oesophageal peristalsis may modify the signal.[3] Airflow changes are detected by means of a pneumotachograph inserted into the circuit, but this has to be removed for suctioning of the airway and may add critically to the dead space of the circuit.[4] Monitoring airway pressure changes is another possible triggering mechanism and this can be performed by addition of a small T piece into the circuit, just proximal to the endotracheal tube. This system we have found easy to use and has none of the disadvantages of the previous two triggering mechanisms we have tested.

The aim of this study was to compare the efficacy of this airway pressure trigger with the commercially available triggering system—that is, the Graseby MR10 respiration monitor.

Patients and methods

Ten preterm infants were studied. All were ventilated for respiratory distress with a median (range) gestational age of 33 (28–35) weeks and median (range) birth weight of 1725 (970–2692) g using the SLE ventilator. Their median (range) postnatal age was 33 (10–300) hours; only one infant was more than 96 hours of age.

Ethical permission for this study was given by the King's College ethics committee.

Patients were entered into the study and changed from conventional ventilation to patient triggered ventilation. They were allocated to receive in random order one of the two triggering systems. The triggering systems involved monitoring either changes in abdominal expansion via the Graseby capsule[1] or airway pressure changes. To monitor changes in abdominal expansion, the pneumatic capsule of the Graseby MR10 respiration monitor was taped onto the patient's abdominal wall in the subxiphisternal position with adhesive tape extending from the abdominal wall above the umbilicus, across the capsule to the skin overlying the xiphisternum and then connected to the monitor. This site of placement was chosen as it had been reported to be the site that most reliably detects respiratory efforts and is least affected by abdominal movement not due to respiratory activity.[5] We also found we could detect the maximum proportion of spontaneous breaths at the subxiphisternal position in comparison to other sites. The output from the capsule then triggered the manual breath control of the SLE ventilator. The signal from the monitor, which recorded changes in capsular volume, was also displayed on a paper record. To monitor airway pressure changes a T piece was inserted into the circuit, just proximal to the endotracheal tube, this was then connected to the ventilator by non-compliant tubing. An airway pressure change of greater than 0·5 cm H_2O was necessary to trigger the ventilator. This permits detection of the fall in airway pressure at the T piece which represents the initiation of spontaneous inspiratory effort by an infant.

Using each trigger system the infants were ventilated at a series of inflation times, 0·24, 0·3, and 0·4 seconds, for 10 minute periods returning between each period to conventional ventilation at the ventilator rate in use before patient triggered ventilation. These inflation times were chosen to equal approximately the expected spontaneous inspiratory time for infants breathing at rates of 60, 80, and 100 breaths per minute, making allowance for the systems delay of up to 40 msecs.[6] No change was made in peak pressure, positive end expiratory pressure, or gas flow rates throughout the study.

During patient triggered ventilation simultaneous recordings were made of flow, volume, ventilator, and oesophageal pressure changes[3] and the output from the Graseby capsule.[5] From the recordings the inflation volume and trigger delay were calculated. At each new inflation time the infant was allowed to settle for the first five minutes. Inflation volume was then calculated as the mean of the inflation volume over the final five minute period at each inflation time. The trigger delay was calculated as the time lag from the start of inspiration, indicated by a negative deflection in the oesophageal pressure trace, and the onset of ventilator breath. The trigger delay was also expressed as a mean of the delays over the last five minutes. The number of spontaneous breaths detected and thus triggering the ventilator were also calculated. This was determined by counting, over the last five minutes of the trace, the number of inspiratory efforts recorded by oesophageal pressure changes, and the number of ventilator inflations. The result was then expressed as a percentage, that is, the number of inflations divided by the number of spontaneous inspirations.

Differences between the two systems at each inflation time were assessed for significance using a paired Wilcoxon rank sum test.

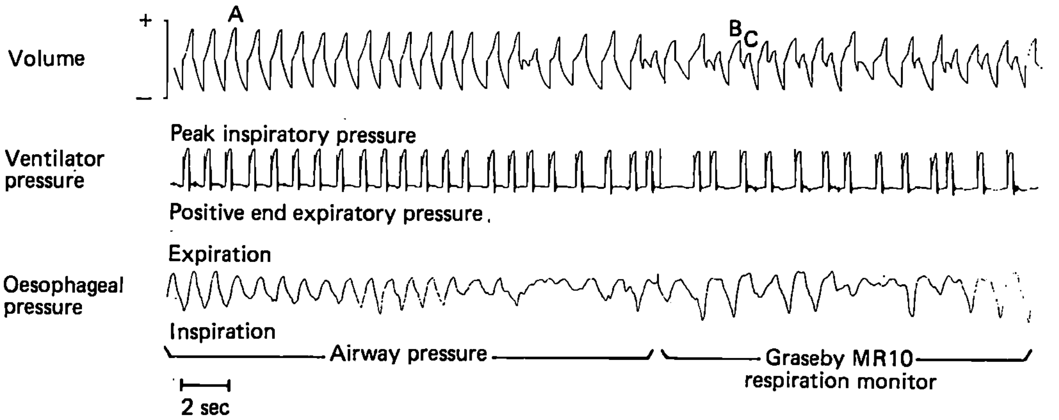
Results

The inflation volume at both 0·24 and 0·3 seconds was significantly larger using the airway pressure compared with the Graseby system (table 1). Lengthening the inspiratory time was associated with an increase in the trigger delay for both systems; however, the trigger delay was

Table 1 Inflation volume and trigger delay at different inflation times. Results are median (range)

Inflation time (seconds)	*Inflation volume (ml/kg)*		*Trigger delay (ms)*	
	Airway pressure	*Graseby MR10 respiration monitor*	*Airway pressure*	*Graseby MR10 respiration monitor*
0·24 (n=10)	5·8 (3·5–10·3)	4·6* (1·7–8·4)	200 (50–400)	300* (100–600)
0·3 (n=10)	6·30 (3·3–11·3)	5·4* (2·0–9·2)	200 (40–300)	350* (100–800)
0·4 (n=8)	6·25 (3·1–10·8)	4·9* (2·8–8·8)	250 (40–550)	550 (100–600)

Because of increased asynchronous effects accurate measurements could only be made in eight of 10 infants at inflation time of 0·4 seconds.
*p<0·05.



Respiratory recording showing the effect of changing from the airway pressure to the Graseby capsule trigger system. Volume is represented in the upper trace (inspiration upwards), ventilator pressure the middle trace, and oesophageal pressure the bottom trace, inspiration represented by a downwards deflation. The inflation time is 0·24 seconds; peak inspiratory pressure and flow rates constant throughout the recording.

Using the airway pressure triggering system, ventilator inflation is coincident with inspiration and is complete by the onset of spontaneous expiration (A). On changing to the Graseby capsule MR10 triggering system, the ventilator breath is frequently delivered at the end of spontaneous expiration because of the prolonged trigger delay, spontaneous inspiration (B) results in a larger tidal volume than positive pressure inflation (C), both display a smaller tidal volume than that seen with the airway pressure trigger system.

Table 2 Association of spontaneous breaths to triggered ventilator. Results are median (range)

Inflation time (seconds)	*Spontaneous respiratory rate (beats/min)*	*Ventilator rate (% of spontaneous inspiratory rate)*	
		Airway pressure	*Graseby MR10 respiration monitor*
0·24 (n=10)	69 (48–132)	100 (89–100)	92 (50–100)
0·3 (n=10)	69 (42–132)	100 (87–100)	89 (50–100)
0·4 (n=8)	63 (36–120)	100* (80–100)	73* (62·5–100)

*p<0·05.

always longer using the Graseby capsule (table 1). The prolonged trigger delay using the Graseby capsule often meant that inflation was delivered late in expiration resulting in a low inflation volume (figure). Using the airway pressure system, all spontaneous breaths were detected in the majority of infants. This, however, was not the case with the Graseby system where a proportion of spontaneous breaths were undetected (table 2). Throughout the study the inspired oxygen concentration was increased if either the transcutaneous oxygen or arterial oxygen tension (PaO_2) fell below 6·67 kPa. This was necessary in three infants using the Graseby trigger but in none using the airway pressure trigger.

Discussion

These results show that the airway pressure device is superior to the Graseby capsule in detecting respiratory efforts. Monitoring of spontaneous respiration using a pneumatic capsule requires considerable skill in placement.[5] Ventilator inflation can cause abdominal excursion, although positioning of the capsule in the subxiphisternal position, as done in this study, reduces the interference from mechanical ventilation in detecting spontaneous respiration.[5] Body movements as well as spontaneous respiratory efforts, however, can also cause changes in abdominal expansion and may, by interference, have resulted in the relatively low detection of respiratory efforts seen in this study. The results of a postal survey we undertook confirmed this finding, 41% of units surveyed complaining of difficulty in achieving optimum placement of the capsule and a relatively poor detection rate. The airway pressure trigger system, in contrast, is much simpler to use, as a T tube is easily placed between the ventilator circuit and endotracheal tube. Its other major advantage is that it does not detect gross movement artefact. The system also appears more sensitive, with virtually every inspiratory effort triggering a positive pressure inflation.

The Graseby system was associated with a significantly longer trigger delay at all inflation times. A long trigger delay has a number of disadvantages. A lag in the onset of the positive pressure inflation will result either in most of the spontaneous inspiration being unsupported by ventilator inflation or in some cases ventilator inflation occurring only after completion of spontaneous inspiration. Such interactions result in diminished inflation volumes compared with those seen when the trigger delay is short, this will reduce minute volume and hence may impair gas exchange. A long trigger delay also means that unless extremely short inflation times are used, with possible deleterious effects on the waveform,[7] positive pressure inflation could extend into spontaneous expiration, provoking an asynchronous interaction and hence increasing airleaks.[8] No infant in this study developed a pneumothorax and short inflation times (maximum 0·4 seconds) were used throughout, but the sample size was too small to make a meaningful statement regarding the influence of patient triggered ventilation on the incidence of airleak.

Although the airway pressure trigger system was superior to the system utilising the Graseby MR10 capsule, even the airway pressure trigger delay may be too long. This delay could be reduced by decreasing the gas flow within the circuit. Such a reduction would diminish the amount of effort the infant would have to generate to exceed the continuous pressure within the circuit and thus exceed the pressure necessary to trigger the ventilator. Reduction in flow would, however, adversely affect ventilator waveform, particularly if short inflation times were being used.[7] We conclude other triggering systems and forms of patient triggered ventilation need to be urgently evaluated. In the meanwhile, we recommend that the airway pressure trigger should be used for neonatal patient triggered ventilation in preference to the Graseby MR10 respiration monitor.

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Effect of body tilting on physiological functions in stable very low birthweight neonates

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Abstract

In babies of very low birth weight (<1500 g) we studied the effect of head up tilting on oxygenation, respiratory rate, heart rate and blood pressure (n=23), on gastric emptying (n=10), and on weight gain (n=6). Head up tilting to 45° achieved the best oxygenation at the angles studied, and decreased the respiratory and heart rates; there was no significant change in blood pressure. Residue in the stomach was also significantly less at 45°, and the neonates' weight gain was higher.

We conclude that nursing stable very low birthweight infants with a higher head up tilt than is conventional may have some advantages.

Except for short periods, humans spend most of their time in the vertical rather than the horizontal position. Although posture is known to affect physiological functions such as lung mechanics and perfusion,[1 2] and gastric emptying,[3] these have mainly been studied in the prone and supine positions and little is known of the effects that postural changes in the vertical plane (tilting) may have on certain functions in either term[4 5] or very low birthweight infants.[6] Stable preterm neonates are conventionally nursed prone with a slight head up tilt, presumably to avoid regurgitation and aspiration of feeds.[7]

The purpose of the present study was to work out systematically the effect of head up tilting at various angles on oxygenation, respiratory and heart rates, blood pressure, gastric emptying, and weight gain in stable, preterm, very low birthweight neonates.

Patients and methods

We studied stable very low birthweight (<1500 g) preterm neonates who had not developed respiratory problems, were being fed normally, and were free from disease. Their gestational age was estimated from maternal dates, ultrasound scans, and a scoring system using physical criteria.[8] Parental consent to participation in the study was obtained on all occasions.

The study consisted of three parts: part 1 was a study of oxygenation at 0°, 10°, 20°, 30°, and 45°, and of respiratory rate, heart rate and blood pressure at 0° and 45°; part 2 a study of gastric emptying at 10° and 45°; and part 3 a study of weight gain at 10° and 45°.

The detailed methods were as follows:

PART 1

To study the variables mentioned previously each neonate was placed in an open air intensive care incubator (Ohmeda) and the tilts achieved by modifying the tilting mechanism of the incubator as required. The neonates were secured in the prone position with a special sling and were supported appropriately. In most instances they were fully clothed and covered with a plastic sheet in order to minimise heat and water losses.

Oxygenation was evaluated using a calibrated transcutaneous electrode (Tc M1 Radiometer) set at 44°C and placed over the interscapular area. The results provided by the instrument used were expressed in mm Hg (conversion factor to SI units: 1 mm Hg=0·133 kPa). Respiratory and heart rates were assessed using a cardiorespiratory monitor (Neoscope, Simonsen and Weel). Blood pressure was measured with a non-invasive oscillometric blood pressure monitor (Dinamap 847, Critikon) and disposable cuffs.

Ten readings of the transcutaneous oxygen monitor were obtained at 30 seconds intervals on each neonate at each tilt (angle). After each change of angle from 0° to 45° and back to 0° there was a 10 minute interval before readings at the new angle were recorded. Readings were obtained in a similar fashion at 0° angle 30 minutes after completing the readings on the return to the 0°.

Together with transcutaneous oxygen readings at 0° and 45°, 10 readings of the respiratory and heart rates at 30 seconds intervals were also obtained on each neonate as well as five readings of the blood pressure at one minute intervals.

Particular care was taken that the readings should be obtained when the neonates were relaxed and asleep. As oxygenation is affected by the state of the neonate, care was taken to try and monitor the infants so they were studied during quiet sleep if possible, using the criteria by Prechtl.[9] No other devices such as electro-oculograms were used. The readings were obtained two hours after the last feed, and the neonates were not disturbed during the assessment. The neonates were not receiving any medication that could potentially affect the respiratory performance or the heart rate such as xanthines.

PART 2

Gastric emptying was assessed at 10° and 45° using the incubator and with the neonates secured in the prone position as described in part 1. The 10° angle was chosen as it closely

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corresponded to the head up tilt used after a feed in many neonatal units. The gastric emptying was assessed by estimating the residue in the stomach 30 minutes after the standard meal and

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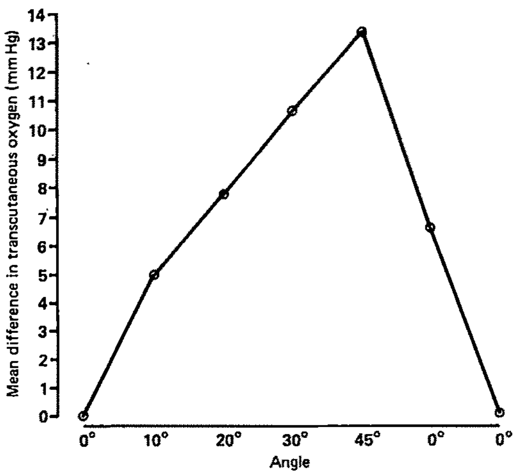
g (range 800–1490), median gestational age 30 weeks (range 26–34) and male to female ratio 1·5:1. From the analysis of the recordings of transcutaneous oxygen tension, heart rate,



Differences in oxygenation expressed as differences among means for the group of 23 neonates at various tilts. The point of reference is the mean oxygenation (0 difference) at the 0° angle. The differences between 0 and 10°=4·6° (95% CI 3·2 to 6·1); between 0 and 20°=7·8° (95% CI 6·1 to 9·5); between 0 and 30°=10·7° (95% CI 8·6 to 12·9; and between 0 and 45°=13·5° (95% CI 11·4 to 15·7)—p<0·01 in all cases (Student's unpaired t test). (Conversion factor to SI units: 1 mm Hg=0·133 kPa.)

Table 2 Percentage gastric residue at 30 minutes at 10° and 45° angles in the 10 neonates studied in part 2

Case No	*Gastric residue*		*Difference between 10° and 45° of original meal*
	10°	*45°*	
1	49·5	47·6	1·9
2	59·7	43·0	16·7
3	35·2	29·0	6·2
4	43·2	40·8	2·4
5	50·7	43·0	7·7
6	38·0	34·8	3·2
7	50·3	38·5	11·8
8	28·1	21·8	6·3
9	40·9	39·5	1·4
10	38·0	35·0	3·0

Table 3 Weekly weight gain during third, fourth, and fifth weeks at 10° and 45°, and differences observed

Week	*Case No and weight gain (g)*											
	1		*2*		*3*		*4*		*5*		*6*	
	10°	*45°*	*10°*	*45°*	*10°*	*45°*	*10°*	*45°*	*10°*	*45°*	*10°*	*45°*
Third	150	0	100	0	140	0	160	0	0	230	0	210
Fourth	0	180	0	200	0	240	0	280	220	0	180	0
Fifth	150	0	150	0	130	0	230	0	0	240	0	190
Differences:												
10°–45°		−30		−100		−100		−120		10		30
45°–10°		30		50		110		50		−20		−10

decrease in gastric residue at 30 minutes (expressed as a percentage of the initial test meal) when the angle of tilt increased (table 2).

Using a paired Student's *t* test the mean of the differences was 6·1 with 95% CI of 2·5 to 9·6 (p<0·01).

PART 3

The weekly weight gain at 10° and 45° was assessed in six neonates only. Median birth weight was 1195 g (range 800–1300), median gestational age 29 weeks (range 26–32), and male to female ratio 1:1. The relatively small number of neonates studied was dictated by the reluctance of parents to agree for their babies to be tilted to a high angle for prolonged periods of time.

Table 3 shows the weekly weight gain at 10° and 45°. In each neonate in either sequence the biggest weight gain was observed at 45°. The difference in weight gain between 10° and 45° ranged from 10 g (case 5) to 120 g (case 4). No side effects were seen and, in particular, no oedema was observed. However a mild nappy rash was seen in four of the neonates at 45°, probably as a result of pressure and irritation of the nappy area.

Discussion

The optimal nursing position for very low birthweight infants has still to be decided. In previous studies the focus was mainly on the effects of postural changes around the horizontal axis of the body. It was shown that the prone position offered certain advantages over the supine mainly in two areas—respiratory performance and gastric emptying. In the prone position ventilation and lung mechanics improved[2] as well as oxygenation[10 11] without the respiratory rate being significantly affected by the change in posture. Yu showed that gastric emptying was quicker in the prone position than in the supine.[3]

The effects that may occur on physiological functions when the body is tilted from the horizontal towards the vertical plane have been little studied in neonates. In 1962 the shift of lung volume with tilting was measured in normal newborn infants[4] to evaluate the effect of gravity in achieving adequate artificial respiration (which had been shown to be possible in adults).[12] It was noted that the respiratory frequency tended to decrease when the infants were tilted head up though no actual data were provided. More recently the effect of postural change on tidal volume, inspiratory and expiratory duration, minute ventilation, and end tidal carbon dioxide tension was studied in term infants.[13] It was observed that both the inspiratory and expiratory times increased in the upright position. These findings are relevant to the decrease in respiratory rate at increased angles that we observed in the present study.

It was also found that tilting newborn infants towards the upright position generally resulted in increased end expiratory lung volume.[13] Recently the effect of tilting on oxygenation on both term and preterm infants was studied by raising them head up to 30° and 20°, respectively. Oxygenation improved with tilting, and this was more pronounced among preterm infants in whom transcutaneous oxygen measurements between 0° and 20° increased by a median value of 1 kPa (7·5 mm Hg) which is roughly equal to our difference of mean transcutaneous oxygen tensions between 0° and 20° (7·8 mm Hg). As shown in the figure oxygenation from 0° to 45° improved in a near linear fashion. A notable difference between that study[6] and our results is that in contrast to our findings Thoresen *et al* observed an upward or downward trend of the transcutaneous oxygen readings depending on whether there was an increase or decrease of tilt.[6] As previously mentioned we

towards the near vertical plane. In the absence of appreciable oedema, the increased weight

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Evaluation of computer generated neonatal discharge summaries

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Abstract

Computer generated and dictated discharge summaries were compared for all 133 babies admitted for intensive and special care during a six month period. Whereas 130/133 (98%) had a computer generated summary, only 94/133 (71%) had a dictated summary. In addition, computerised summaries were completed at discharge, but there was a delay up to 26 weeks for dictated summaries. Dictated summaries had more items of basic data missing but were more readable. A main diagnosis was missing in only 5/95 (5%) of dictated and 1/130 (1%) computerised summaries. Of the computer generated summaries, 114/133 (86%) were suitable to give to parents.

Satisfactory discharge summaries for babies requiring intensive or special care can be generated with an on line computer system.

Continuity of care for babies discharged from neonatal units relies on good communication between hospital and community health professionals. Traditionally this has been achieved by doctors dictating discharge summaries, which are then typed and circulated. Compiling summaries for babies who have been in intensive care can be time consuming and arduous, especially when there have been several weeks between the baby's acute illness and his discharge from hospital. Selecting information without omitting important items is hampered by difficulty in finding the relevant information among copious notes, and the summary then needs to be typed, corrected, and distributed.

We have developed a neonatal information system into which data are entered on line by paediatricians who benefit from the automatically generated discharge summary. As the neonatal module is an integral part of an established maternity system—the St Mary's Maternity Information System—registration information and details of the pregnancy, delivery, and birth are transferred directly, avoiding re-entry of these data.[1 2] The system also provides data for neonatal, obstetric, and administrative audit and generates ICD (International Classification of Diseases) codes for all neonates.

The St Mary's Maternity Information System is installed in all maternity units in the North West Thames Health Region, and covers 40 000 deliveries each year. The neonatal module was piloted in 1988 in the neonatal unit at St Mary's Hospital, and more recently in Hillingdon and Ealing hospitals.

We have conducted an initial evaluation of the computer generated summaries by comparing them with dictated summaries. We noted the number of summaries and the time it took to complete them, and compared a number of basic data items and the diagnoses for each baby. We also looked at their readability. As we planned to give a copy of the summary to the parents, we also assessed whether or not we considered the summaries suitable for them.

Materials and methods

DATA COLLECTION

Clinical data about any infant requiring intensive or special care are entered into the computer by paediatric staff who select relevant systems from a menu (table 1). To minimise the need to enter negative answers, a branching method of data entry is used so that further information is only requested when relevant, only systems with abnormalities are selected, and only important problems are entered.

For short stays in the baby unit all the clinical information can be entered when the baby leaves the unit. For complicated patients who stay a long time information is entered at least weekly to ensure its accuracy.

At discharge a list of diagnoses linked to ICD codes is generated by the computer. This is checked, amended as necessary, and the diagnoses ranked in order of importance by the paediatrician. In addition, advice on pertussis immunisation is entered and a statement is made about the baby's neurological and ophthalmological status at discharge. Free text can be added to the discharge letter; this is particularly useful for expanding social problems and discussing prognoses that do not lend themselves to computerisation, but it is discouraged for medical problems.

When data entry is complete the discharge summary is generated. Copies are printed for the neonatal notes, general practitioner, midwife or health visitor, or both, and the obstetric notes. A copy may also be printed for

Table 1 Systems menu

Respiratory
Birth asphyxia/trauma
Cardiovascular
Neurological
Jaundice
Fluids, metabolic, and drug withdrawal
Nutrition, gastrointestinal, and bones
Haematology
Infection and temperature
Urogenital
Congenital abnormalities/syndromes and skin
Social factors
Additional comments
Infant death

the mother. The data are also available for audit, and monthly and annual activity reports have been designed. The computer is also used by nursing staff to generate the daily bed state, which includes details of the level of care each baby is receiving.

METHODS

During the six month period from August 1988 to January 1989 when the computer system was being piloted, discharge summaries were dictated by the senior registrar using information from the clinical notes. These were then typed by a secretary who kept a record of the date the summary was typed, and filed a copy for the study. Concurrently data was entered on computer by the paediatric senior house officers on a terminal in the baby unit, and the summaries were generated when the babies were discharged. These were then also filed and kept for this study. They were not available when the summary was dictated nor were they distributed to general practitioners. Dictated summaries and those generated by computer were compared with the notes by a doctor (AS) with neonatal experience but who was not working in the neonatal unit during the study period, and therefore had no personal knowledge of the patients.

The following assessments were performed:

The time of completion of summaries

The summaries were matched with admissions to the unit to find out how many summaries were not completed.

Basic data

A number of items of information were identified that we considered should be included in all summaries (table 2). Each summary was checked to see how many items were missing.

Accuracy of clinical data

The notes were examined and a list of the main diagnoses was made for each baby. As no strict criteria for inclusion or exclusion could be made, personal clinical judgment was used to identify the most important diagnoses. These were checked against those listed in the dictated and computerised summaries. In addition, the five most complex notes were selected and all items of data were listed and compared.

Table 2 Items that should be included in a discharge summary

Registration information
Dates of admission and discharge
Reason for admission
List of diagnoses
Mode of delivery and reason for intervention
Apgar scores
Gestation and sex
Birth order if multiple birth
Birth weight and birth head circumference
Conditions requiring treatment
Congenital abnormalities
Treatment given in hospital
Treatment at discharge
Prognosis and residual disability at discharge

Readability

A measure of readability was made for each summary on a scale of 0 to 10. Readability was judged according to how well the information about the baby could be assessed by reading through the summary. No strict criteria for this measure could be laid down.

Suitability of summaries for parents

An assessment was made of whether the computer summary was suitable for the parents. Summaries were deemed unsuitable if they were too technical or if it was thought that they might upset parents because the information was not imparted in a sensitive way.

Results

One hundred and thirty three infants were discharged or died between August 1988 and January 1989 and their notes and summaries were compared.

Time of completion of summaries

Whereas 130 (98%) had a completed computer discharge summary only 94 (71%) had a dictated summary. Computerised summaries were completed at the time of discharge from hospital, but the completion times for dictated summaries ranged from one to 26 weeks after discharge.

Basic data

Basic data that were missing or incorrect in the 94 dictated and 130 computer discharge summaries are shown in table 3. Data relating to birth weight, mode of delivery, and Apgar

Table 3 Basic data omitted or incorrect in dictated and computerised summaries. Figures are expressed as number (%)

	Dictated (n=94)	*Computerised (n=130)*
Missing data in discharge summaries:		
Diagnoses	5 (5)	1 (1)
Birth weight	33 (35)	0
Gestational age	17 (18)	1 (1)
Head circumference at birth	85 (90)	11 (9)
Mode of delivery	14 (15)	0
Reason for intervention (n=42)	2 (5)	39 (93)
Apgar scores	11 (12)	0
Reason for admission to special care baby unit	3 (3)	2 (2)
Weight at discharge	61 (65)	6 (5)
Head circumference at discharge	70 (75)	13 (10)
Feeding at discharge	65 (69)	5 (4)
Discharge destination	63 (67)	3 (2)
Treatment on discharge (n=36)	12 (33)	1 (3)
Immunisation recommendations	19 (20)	6 (5)
Date of follow up appointment (n=47)	46 (99)	6 (13)
Total	506	94

[redacted]

scores are transferred from the maternity system and were complete in the computerised summaries. Details transferred from the obstetric system are partly validated at the time of entry, and a recent independent validation of all items included in the maternal discharge summaries during a three month period at this hospital showed an accuracy of over 99%. As the reasons for operative delivery are often complex, they are not routinely recorded on either the obstetric or the neonatal computer. This meant that unless the reason for intervention was mentioned in the additional comments there was no record on the computerised summaries. Discharge information was often omitted from the dictated notes, and the babies' weight at discharge was omitted in 61 of the 94 (65%) summaries as it was recorded in a different section of the babies' records. Whether pertussis immunisation was contraindicated was omitted from 19 of the 94 dictated summaries (20%), compared with six of the 130 computerised summaries (5%). In a number of the dictated summaries there were gross errors in the data. In one the baby's sex was incorrectly documented, in six the mode of delivery was wrong, and in two the birth weights were wrong.

In 21 of the dictated summaries there was no indication either by name or pronoun of the sex of the infant.

Accuracy of clinical data

Five of the diagnoses were missing in the 94 dictated summaries and one in the 130 computerised summaries.

Readability

Readability scores showed that the dictated summaries were more readable, with a median score of 8, compared with 6 for the computer generated summaries.

The dictated summaries gave a more complete impression of the events leading up to birth, the sequence of events in the neonatal period, and the long term prognosis especially of preterm infants with long, complex medical histories. This difference was less obvious when paediatricians had used the facility to add additional comments to the computerised summary. In the 130 summaries reviewed, 28 (22%) had additional comments entered, 52 (40%) would have been improved if additional comments had been entered, and 50 (38%) summaries did not require any further information. It was thought that the computerised summaries would also have been easier to read with a better quality printer. Although dictated summaries tended to list events in chronological order, which made them easier to follow, it was harder to find specific information without reading the entire summary.

Suitability of summaries for parents

It was thought that the computerised summary was suitable in its present form for 114 (88%) of infants. They were considered unsuitable for parents when the babies were discharged to foster parents as they contained too many maternal details. The summaries are rather technical and brusque and it was thought that the lack of sympathy could distress parents of the nine babies who died, or the four with major chromosomal abnormalities.

Discussion

The primary objective of the design of the system was to produce a summary containing all the important information required when the baby left hospital. The summary should contain an accurate account of the baby's major problems in hospital, and any items of relevance to long term care. Whereas virtually all (98%) of the computer generated summaries were done at discharge only 71% of babies admitted to the baby unit had a dictated summary with delays of up to 26 weeks. As well as depending on the diligence of the registrar, delay sometimes occurred because the baby was discharged from the postnatal wards and by the time the notes had been returned to the neonatal unit for dictation they were needed in clinics. Holidays, study leave, and change of staff further exacerbated the delay. Had the summaries been dictated by the senior house officers it is likely that more summaries would have been completed and some units do demand, and achieve, typewritten summaries before discharge. Dictating summaries for babies who have undergone intensive care is time consuming, however, and at busy times it is often difficult to do this before discharge.

The superiority of the computer in recording basic data at birth and discharge was readily apparent. In 21 of 94 (22%) dictated summaries there was no indication of the sex of the infant. Computers can enforce greater completeness of data, and can be programmed to ensure that advice on routine procedures such as pertussis immunisation is included.

The lists of diagnoses generated by the computer were slightly more complete than those in the dictated summaries. Listing the diagnoses, linked to ICD codes, in order of priority enables the system to comply with Department of Health requirements.

No attempt was made to check in detail the accuracy of the data entered by the paediatrician. Only information of clinical importance should be entered and this depended on the discretion of the person entering the data; each item of data needs to be carefully defined. In addition, the reliability of the data collected needs to be checked—for example, for babies receiving artificial ventilation several paediatricians have requested that the maximum inspired oxygen concentration, peak ventilatory pressure, and maximum ventilatory rate be recorded, but we have found that these data cannot be collected accurately. Should they be the highest ever employed, or should they refer to values once the baby is stabilised? Further development is required to decide which items of data should be collected and which can be dispensed with.

Dictated summaries were usually more readable and gave a chronological sequence of events. They also provided more comprehensive information about social circumstances and prognosis. They often contained much superfluous information, however, and it is possible that long and detailed summaries are not always

been overprotective. Particular care needs to be taken when babies have died, have a major congenital abnormality, experienced birth asphyxia or intraventricular haemorrhage, or when they have been born to drug users, to make sure that the summaries correspond with what parents

[redacted]

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Neonatal Haemophilus influenzae infections

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Abstract

Nine cases of neonatal *Haemophilus influenzae* septicaemia were recorded in Finland during 1985–9; incidence was 2·8/100 000 live births, and 1·6% of all cases of neonatal septicaemia. The onset of the disease was early in all cases, ranging from 0–6 hours after delivery. Seven of the infants were preterm and three died (overall mortality 33%). *H influenzae* was isolated from blood in seven of the cases, and in two neonates with clinical signs of septicaemia it was found on several surface sites and the placenta. One of the eight strains of *H influenzae* was capsular type b and biotype I, the rest being nontypable—a distribution similar to those previously reported. Four of the uncapsulated strains were of biotype III, and three were of biotype II. None of the strains of *H influenzae* was of biotype IV, which has been reported to be characteristic of neonatal and genital isolates of *H influenzae*. All nine mothers had some sign of infection at the time of or shortly after delivery. *H influenzae* was isolated from five mothers: from the blood (n=1) or from the placenta or cervix (n=4).

The use of intrauterine devices may be a possible risk factor for neonatal *H influenzae* infections; two of the mothers had such devices in place during their pregnancies.

Neonatal *Haemophilus influenzae* infections were once thought to be rare, but during the past decades an apparent increase of such infections has been reported.[1 2] *H influenzae* infections have been found mainly among preterm, low birthweight infants,[2–6] and are characterised by the early onset of symptoms and the fulminant course of the disease.[2 6] It has been suggested that these infections may have started during pregnancy and are the cause of the premature birth.[7] The mortality associated with neonatal *H influenzae* septicaemia is high, up to 86% having been reported.[3 6]

Most (80–90%) of the strains of *H influenzae* that cause neonatal septicaemia are nonencapsulated,[8] whereas 95% of strains that cause invasive disease among older children are capsular type b.[9] The neonatal strains and the strains that colonise the female genital tract have been reported to be predominantly biotype IV, and seldom biotype II or III,[8 10] whereas most of strains with the type b capsule are of biotypes I or II.[11–13]

A nationwide intensified surveillance of invasive infections in children (including neonates) was started in Finland in 1985[14] as a part of a trial of the efficacy of a vaccine against *H influenzae* capsular type b.[15] We report the results of a five year prospective follow up of neonatal *H influenzae* infections in Finland and describe the clinical and bacteriological features of nine cases of neonatal *H influenzae* infection.

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Patients and methods

In the nationwide surveillance all bacterial isolates from blood, cerebrospinal fluid, or other sterile body sites of children (0 to 15 years of age) with invasive disease were sent to the National Public Health Institute from the 25 microbiological laboratories in Finland. In addition, if a neonate (defined as an infant less than 28 days of age) was thought clinically to have septicaemia and the same bacterial species was isolated from many surface sites (for example, ear, umbilicus, or throat) and the placenta, this strain was included in the collection. The identification of strains was confirmed at the National Public Health Institute and samples were stored at −70°C. The laboratory records from the years 1985–9 in each of the laboratories were also examined retrospectively to find possible omissions from the collection. Detailed data about the patients and their mothers were collected from the hospital records.

The capsular types (a–f) of the strains of *H influenzae* were ascertained by a coagglutination technique.[11] Strains were designated to biotypes I-VIII on the basis of their urease and ornithine decarboxylase activity and the production of indole.[16] Production of β-lactamase was tested by the clover leaf method[17] or the acidometric assay, or both.[18]

Results

CLINICAL FEATURES AMONG THE NEONATES

During the five year study period from January 1985 to December 1989, nine neonates with *H influenzae* septicaemia were recorded. During that time there were 317 673 live births in Finland, giving an annual incidence of 2·8/100 000 live births. All nine cases were identified by the prospective surveillance, and no further cases were found through the retrospective evaluation of laboratory records. During the same period the surveillance yielded a total of 547 cases of invasive neonatal disease, with positive bacterial cultures from blood, cerebrospinal fluid, or any other usually sterile body fluid. *H influenzae* comprised 1·6% of all neonatal infections. In seven neonates *H influenzae* was isolated from the blood and in two cases from several surface sites as well as from the placenta. None

Table 1 Clinical features and bacteriological findings in nine infants with H influenzae septicaemia

Case No	Sex	Gestation (weeks)	Birth weight (g)	Apgar score		Time from birth to onset of symptoms (hours)	Outcome	H influenzae		
				1 min	5 min			Site of isolation	Capsular type	Biotype
1	Female	25	810	4	3	0	Died	Blood	Not typable	III
2	Male	26	830	3	3	6	Recovered	Blood	Not tested	Not tested
3	Female	28	1315	5	6	0	Died	Blood	Not typable	II
4	Male	29	1735	6	7	0	Died	Blood	Not typable	III
5*	Male	30	1420	7	9	0	Recovered	Blood	b	I
6	Female	35	2410	1	4	0	Recovered	Ear, umbilicus, placenta	Not typable	III
7	Male	35	1760	8	9	1	Recovered	Blood	Not typable	II
8	Male	40	3130	7	8	0	Recovered	Throat, ear, placenta	Not typable	III
9	Male	41	3730	9	9	0	Recovered	Blood	Not typable	II

*Home delivery.

of the nine cases had signs of meningitis, and the cerebrospinal fluid was not cultured from any of the patients.

The onset of disease was early in all the cases, ranging from 0–6 hours after delivery (table 1). Seven patients were preterm (gestational age range 25–35 weeks) and weighed less than 2500 g at birth. All three deaths occurred among the preterm neonates.

H influenzae septicaemia was accompanied by raised ($>30\times10^9$/l) white cell count in two, by leucopenia ($<8\times10^9$/l) in three, and by normal values in four of the patients. All six neonates from whom serum C reactive protein concentrations were available had increased values ($\geqslant 20$ mg/l). Respiratory distress syndrome was noted in five neonates, all of whom were preterm (gestational age 25–30 weeks) (table 1).

Only one child had septicaemia caused by type b *H influenzae* (case 5, table 1). This was the mother's third pregnancy and delivery. She had an intrauterine device in place and was not aware of the pregnancy until the delivery started at 30 weeks' gestation. The child was born at home with a nurse in attendance. Immediately after birth (the labour lasted 1·5 hours) the child was transferred to hospital. On arrival he had breathing difficulties with hyperventilation, bradycardia, hypotonia, and hypothermia. After intubation, and correction of his haemodynamic state, his condition improved. After blood had been taken for culture, antimicrobial treatment with penicillin G and netilmicin was started. Mild respiratory distress syndrome developed and he required two days on the ventilator. Antibiotic treatment was stopped on day 3, before the results of the blood culture were available. As no further signs of septicaemia developed, and the white cell count and C reactive protein remained normal, however, the antibiotic treatment was not started again. The child recovered uneventfully and his development has been normal.

ISOLATES OF H INFLUENZAE FROM NEONATES

Isolates of *H influenzae* were available from eight neonates (table 1). In only the above mentioned case was the isolate of capsular type b. It was of biotype I and produced β-lactamase. The rest of the isolates were non-typable. Four of these were biotype III and three biotype II. None of the non-typable isolates produced β-lactamase. The antimicrobial treatment given was according to the regimens in the respective hospitals, and in most cases was a combination of netilmicin and ampicillin.

CLINICAL FEATURES AND ISOLATES OF H INFLUENZAE AMONG THE MOTHERS

Seven of the nine mothers had signs of infection before or during delivery (table 2), and the remaining two (cases 1 and 4) had raised white cell counts or C reactive protein concentrations, or both. In five cases *H influenzae* was isolated from blood, from the placenta, or from the cervix. Unfortunately the strains were not preserved for typing. In three cases there was premature rupture of the membranes. The role of

Table 2 Details of mothers of the nine infants with H influenzae septicaemia

Case No	Age	Parity	Premature rupture of membranes (hours)	Delivery		Signs of infection	White cell count		C reactive protein concentration		Site of isolation of H influenzae (strains not available for typing)	Used intra-uterine device
				Mode	Length (hours)		$\times10^9$/l	Day of measurement	mg/l	Day of measurement		
1	16	I	No	Vaginal	5·5	None	13·3, 11·1	Not recorded	57, 42	4, 5	Not known	No
2	27	II	48	Vaginal	4	Choriamnionitis	60	0	19·7	0	Cervix	No
3	38	III	No	Caesarean section	Not applicable	Septicaemia	11·9, 31·2	Not recorded	91, 110	0, 1	Blood	Yes
4	30	II/III	No	Vaginal	0·5	None	34·3	Not recorded	12	0	Not known	No
5*	23	III	No	Vaginal	1	Chorioamnionitis	9·1	3	Not measured		Not known	Yes
6	22	II	No	Vaginal	Not known	Chorioamnionitis, sinusitis two weeks before (ampicillin treatment during delivery)	29·5, 14·5	Not recorded	>40, >40	0, 3	Placenta	No
7	19	II	No	Vaginal	4	Amnionitis	Not measured	Not measured	Not known	No		
8	23	I/II	14	Vaginal	6·5	Amnionitis	14·2, 19·8, 12·2	Not recorded	165, 123, 78	0, 1, 3	Placenta, cervix	No
9	22	I	36	Caesarean section	Not applicable	Chorioamnionitis	11·4, 12·3	Not recorded	17, 195	0, 1	Placenta	No

*Home delivery.

White cell count		*C reactive protein concentration*		*Respiratory distress syndrome*	*No of days in respirator*	*Antimicrobial treatment*
×10⁹/l	*Day of measurement*	*mg/l*	*Day of measurement*			
3·2, 6·4	0, 1	Not measured		Yes	2	Not known
1·1, 24·4	0, 2	Not measured		Yes	10	Netilmicin, ampicillin
10·8	1	Not measured		Yes	2	Netilmicin, ampicillin
6·7, 0·8	0, 0	21, 51	0, 0	Yes	1	Netilmicin, ampicillin
17·5	2	45, <10	0, 3	Yes	2	Netilmicin, penicillin G
12·3, 33·1	0, 1	102	1	Not known	1	Gentamicin, penicillin G
2·6, 13·3	0, 4	<18, 140	0, 2	Not known	6	Netilmicin, ampicillin
5·1, 14·1	0, 2	0, 171	0, 1	Not known	Not known	Netilmicin, amoxycillin
23·7, 11·8	1, 2	51	1	Not known	Not known	Netilmicin, ampicillin

intrauterine devices emerged as a possible risk factor in neonatal *H influenzae* infections, as two of the mothers had devices in place during their pregnancies.

Discussion

In the United States between 2·6% and 7·9% of all neonatal septicaemias are caused by *H influenzae* and an apparent increase of these infections has been reported during the past decades.[1 2 8] In addition, a report describing neonatal septicaemia in seven centres in Finland during a 10 year period covering roughly 43% of all deliveries in Finland was published in 1989.[19] In that study, a total of six cases of *H influenzae* septicaemia were found, three during each five year period, 1976–80 and 1981–5.

The present study describes a nationwide study for the five year period 1985–9 in which nine cases of neonatal *H influenzae* infection were identified by intensified prospective surveillance. It seems therefore that all cases of neonatal *H influenzae* infection from that period are included. Compared with the previous report from Finland there seems to have been no increase in the incidence neonatal *H influenzae* infections during the past 15 years, and *H influenzae* infections account for only a minority, 1·6%, of all neonatal septicaemias.

Our study includes two cases in which *H influenzae* was not isolated from blood, but from several surface sites as well as from the placenta. Both these neonates had clincal signs of septicaemia, there was a raised white cell count ($33 \cdot 1 \times 10^9$/l) in one case and raised concentrations of C reactive protein in both cases (171 mg/l and 102 mg/l, respectively). The value of culturing a *H influenzae* from surface sites is supported by the study in which 70% of neonates with blood cultures growing *H influenzae* also had positive cultures from surface sites.[20]

All the six patients in whom C reactive proteins concentrations were assayed had increased values. In contrast to a previous report in which it was suggested that the measurement of C reactive protein is no use in the diagnosis of neonatal septicaemia,[21] our results suggest that in *H influenzae* septicaemia high concentrations of C reactive protein do occur, and the measurement of the concentration might be useful.

The clinical course of neonatal *H influenzae* infection was characterised by prematurity, the presence of maternal complications, and high neonatal mortality, as has been reported previously.[2–6] In the present series all the cases developed early—that is, at delivery (seven cases) or within a few hours after delivery. This compares with earlier reports in which 85% of cases were of early onset defined as less than 24 hours after delivery.[2 6]

All the mothers in the present study had some signs of infection at the time of, or shortly after, delivery and *H influenzae* was isolated from 56% of them. Premature rupture of membranes was not a serious predisposing factor to neonatal infection as previously suggested.[3 5] These findings support the hypothesis that neonatal *H influenzae* infections are transmitted from the mother, that the infection starts before birth, and that it could be the cause of premature birth.[1 3 6–8] Two of the mothers had interuterine devices in place, a possible predisposing factor for *H influenzae* infection. An association between intrauterine devices and neonatal *H influenzae* infection has previously not been reported, and there are only few case reports about other pathogens (*Escherichia coli* and *Candida albicans*) associated with neonatal septicaemia and intrauterine devices.[22 23]

Seven of the eight neonatal isolates of *H influenzae* in the present series were non-typable, and there was one isolate of capsular type b, a finding similar to previous reports.[8] The relative absence of type b isolates causing neonatal *H influenzae* infections is thought to be the result of maternal anti-*H influenzae* type b antibodies, which last for roughly the first six months of life; after this age the incidence of type b *H influenzae* infections increases appreciably.[24] In addition, the colonisation of the female genital tract with type b *H influenzae* is rare: carriage of *H influenzae* is about 1%, and of the isolates only a few are type b.[20] Preliminary results indicate that serum antibodies against non-typable *H influenzae* are relatively high among female population of child bearing age (M Leinonen, personal communication). This may partly explain the rarity of neonatal *H influenzae* infections despite the 1% vaginal carriage rate of non-typable *H influenzae*.[20]

None of the non-typable isolates of *H influenzae* were of biotype IV, which has been reported to account for up to 38% of neonatal isolates in the United States.[8 10] Geographical differences have also been found in the comparison of isolates of type b *H influenzae* that cause invasive infections among older children, using several subtyping methods including biotyping. In these infections biotypes I and II both account for about half the isolates in Finland, while biotype I predominates (90%) in the United States and The Netherlands.[11–13] Geographical differences have also been found among strains of the most common neonatal pathogen, group B streptococcus, with serotype III accounting for a third of cases of early onset in the United States compared with only 10% in Finland.[25 26] It has been suggested that there could be a difference in the virulence of these strains, leading to a predominance of group B streptococcal disease of early onset and a relative absence of disease of late onset in Finland,[26] a similar difference to that found in the present study of neonatal *H influenzae* septicaemia. It might be that the emergence of biotype IV *H influenzae* as a genital pathogen in the United States is the cause for the increase of neonatal *H influenzae* infections.

In Finland these strains (or this clone) do not occur, and thus the incidence of neonatal *H influenzae* infections has been stable. This clone may also have special properties of virulence, as has been documented for *H influenzae* type b isolates of a certain clone characteristic to Finland.[27]

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Neonatal diaphragmatic paralysis caused by chest drains

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Abstract

A boy delivered at 32 weeks' gestation developed bilateral pneumothoraces that required multiple chest drains. He was dependent on the ventilator for 52 days because of bilateral diaphragmatic paralysis. Electrophysiological studies confirmed phrenic nerve damage. He eventually made a full recovery. It is likely that this damage was caused by the insertion of the chest drains.

The problem of the baby who refuses to breathe effectively after ventilation is one familiar to neonatologists. When the problem is not one of prematurity, the difficulty is deciding whether the cause of underbreathing is central or neuromuscular. We present a case of paralysed diaphragms where the cause was iatrogenic.

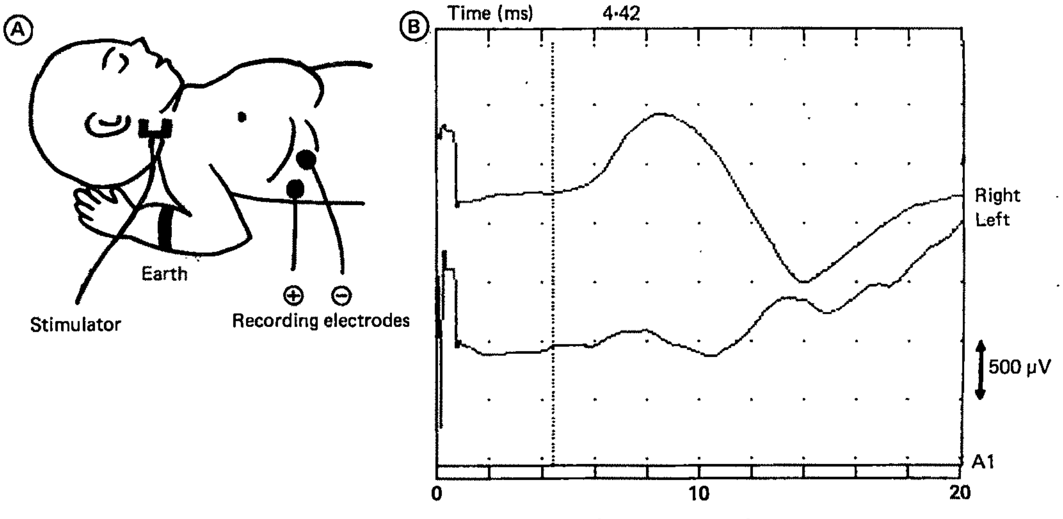
Case report

A boy was delivered at 32 weeks' gestation by caesarean section because of maternal pre-eclamptic toxaemia. He weighed 1810 g, and his Apgar scores were 8 at 1 minute and 9 at 5 minutes. He rapidly became tachypnoeic and by 4 hours of age had been intubated and was requiring full ventilation. Chest radiography confirmed moderate respiratory distress syndrome. Poor synchrony with the ventilator necessitated paralysis with atracurium for 48 hours. When the paralysis was stopped he developed pneumothoraces, first on the left and then on the right. Over the next four days three chest drains were put in the right and two in the left pleural cavities. The air leaks sealed and by day 7 he required only minimal ventilation. Any attempt at weaning from the ventilator, however, resulted in profound hypoxia. Although his limb movements were normal, it was clear that his respiratory excursion was poor.

The differential diagnosis lay between an acquired bilateral diaphragmatic paralysis or a congenital neuromuscular condition. Although the latter seemed unlikely in view of the generalised adequacy of movement and tone, edrophonium was given as a test for myaesthenia gravis. After the edrophonium had been given his condition deteriorated and temporarily he needed more respiratory support. Ultrasonography of the diaphragms during spontaneous breathing showed poor diaphragmatic excursion, which was confirmed on fluoroscopy.

In view of this, phrenic nerve conduction was carried out by stimulating each side of the neck using a stimulation of 0·1 milliseconds duration at 1 Hz. Recording was performed with silver/silver chloride disc electrodes over the sixth intercostal spaces in the anterior axillary line. (figure). This was carried out on day 19, and there was no recordable potential on either side. The right median nerve action potentials were normal.[1] This excluded generalised neuropathy and localised the lesion at the phrenic nerve bilaterally.

He was ventilated for a total of 52 days with frequent episodes of bradycardia and anoxia. These episodes became less frequent, and when he was eventually extubated fluoroscopy showed normal diaphragmatic movement on the right but diminished movement on the left.



Phrenic nerve conduction studies showing (A) technique and (B) the recording at the age of 3 months.

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Phrenic nerve studies showed that the right phrenic nerve was excitable with a latency of 3·3 milliseconds but the evoked muscle action potentials were small (100 microvolts). The left side remained unexcitable. The baby was discharged home before diaphragmatic movement had returned to normal. Three months later he was thriving without respiratory problems. The phrenic nerve studies showed a normal diaphragmatic response on the right (4·4 milliseconds, 1·5 microvolts). The left phrenic nerve was excitable even though the response was small (4·4 milliseconds, 200 microvolts) (figure).

Discussion

The phrenic nerve studies on this neonate were of great help. The median mixed nerve action potentials and edrophonium (Tensilon) test excluded generalised neuropathy and myaesthenia gravis, and serial phrenic nerve studies confirmed that the bilateral diaphragmatic paralysis was the result of phrenic nerve dysfunction. Of the cases of paralysed diaphragms in the newborn period, 80–90% are the result of brachial plexus injury and 5% of all brachial plexus injuries have associated diaphragmatic paralysis.[2] Of traumatic causes, damage during cardiac surgery is a well recognised problem.[3] The treatment of a pneumothorax by insertion of a chest drain is an all too common experience in a neonatal unit. Complications of this procedure include perforation of the lung parenchyma,[4] but surprisingly, phrenic nerve injury secondary to insertion of a chest drain has been reported only twice to our knowledge, and on both occasions the paralysis was unilateral.[5 6]

Drainage tubes placed deep in the chest carry a risk of injury to the phrenic nerve.[6] It was clear from reviewing the series of radiographs that two basal and two apical chest drains had impinged on the baby's mediastinum. The phrenic nerves run down in the mediastinum over the pericardium, and theoretically any of the four drains could have caused nerve damage.

The message is that diaphragmatic paralysis may be a cause of failure to wean a baby from the ventilator who has had bilateral chest drains inserted. If the chest drains are reaching the mediastinum, they should be withdrawn fractionally, even if they are functioning well. When the cause of underbreathing is not clear, phrenic nerve conduction studies are helpful.

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Ciliary beat frequency in newborn infants

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Abstract

The ciliary beat frequencies of 31 newborns and 14 adults were measured in vitro by a photodiode method at body temperature (37°C). The mean (SD) neonatal ciliary beat frequency (12·7 (0·82) Hz) was faster than that in adults (11·1 (0·84) Hz) ($p<0·01$). Increased ciliary beat frequency may be advantageous during the neonatal period.

Ciliary dyskinesia should be considered in any neonatal patient or infant with unexplained respiratory distress. Buchdahl showed that when a child's respiratory problems are linked to ciliary dyskinesia, respiratory symptoms often start in the perinatal period.[1] Ciliary problems can be diagnosed by structural or functional studies.

Ciliary ultrastructural examination may, however, be normal despite impaired function as defined by a reduction in ciliary beat frequency. The saccharin test of ciliary function requires cooperation and can not be carried out in young children,[2] so in vitro measurement of ciliary beat frequency seems to be the most effective screening procedure for ciliary function in this age group. A reference range for ciliary beat frequency had not been defined for children.

The aims of our study were to determine a reference range of ciliary beat frequency in newborns, and to compare this with adult values.

Patients and methods

Thirty well newborn children less than 5 days of age (13 girls and 17 boys) were studied between September 1989 and February 1990. Fourteen adult volunteers mean (SD) age 21 years who had not had an upper respiratory tract infection for at least six weeks were also studied. All were non-smokers and none had a history of chest disease.

A sample of ciliated epithelium was obtained from the inferior turbinate of the nose with a cytology brush without anaesthesia. Cilia were suspended in 1 ml of medium 199 cell culture fluid and a sample of this examined in a sealed microscope slide cover slip chamber. The preparation was placed on a heated microscope stage maintained at 37°C and allowed to equilibrate for 10 minutes. Specimens were examined with an inverted phase contrast microscope (Leitz-Vetzlor Orthoplan) at a magnification of 100 with oil immersion. A video camera (Hitachi QP-140E/K) projected the image on to a video display unit. The resulting magnification was ×2000. A video enhancer circuit was added to the circuit to accentuate ciliary outlines.

Ciliary beat frequency was measured by holding a PIN photodiode probe over the moving ciliary edge. Fluctuations in intensity from the moving cilia were converted, amplified, and filtered to generate a voltage wave form that was displayed on the screen of a digital storage oscilloscope using a method described by Teichtal *et al.*[3] The wave forms captured were plotted on to a chart recorder. The ciliary beat frequencies from at least 10 separate cilial edges were recorded from each patient.

To assess the variability with time, nine newborn infants had further biopsies 24 hours later and the ciliary beat frequency measured again. The observer was unaware of the source of the second sample.

CALIBRATION OF THE PHOTODIODE

To calibrate the PIN photodiode amplifier and recording system, a BBC microcomputer program was written to produce a flashing cursor on the video monitor. The program could produce a range of frequencies from 2·5 to 35 Hz by varying the time for which the flashing cursor was on or off in integer steps of 0·1 seconds. These frequencies were measured by the photodiode system and the results obtained compared with the frequency generated by the microcomputer.

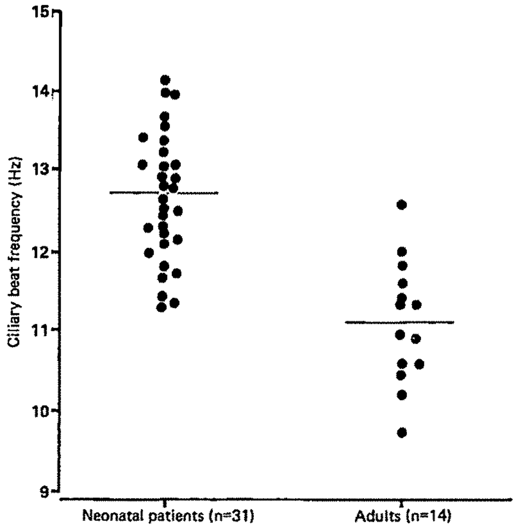
STATISTICAL ANALYSIS

The unpaired Student's t test was used to compared the results of adult and neonatal ciliary beat frequencies. An intraclass correlation coefficient was calculated to assess reproducibility.[4]

Ethical approval was obtained from the Nottingham Hospitals ethics committee.

Results

The mean (SD) ciliary beat frequency was 12·7 (0·82) Hz for the neonatal group and 11·1 (0·84) Hz for the adult group ($p<0·01$) (figure). The intraclass correlation coefficient was 0·85 ($p<0·002$) between samples taken from the nine neonatal patients on two consecutive days. An intraclass correlation coefficient of 0·99 ($p<0·0001$) was obtained when the signal from the BBC computer was compared with the frequency detected by the photodiode system.



Ciliary beat frequency in 14 healthy adults and 31 newborn infants.

Discussion

When examined at body temperature the cilia of newborn infants had a significantly higher beat frequency than those of adult volunteers. This increased frequency may aid mucus clearance in newborn infants and therefore be advantageous.

The photodiode system accurately recorded frequencies from 2·5 to 35 Hz. The high intraclass correlation coefficient suggests good reproducibility in measurements of ciliary beat frequency when cilia from the same infant were studied on consecutive days.

It is difficult to explain increased ciliary beat frequency by changes in ciliary ultrastructure, as a previous study showed no ultrastructural differences between neonatal and adult cilia on electron microscopy.[5] This suggests that a difference in metabolism may account for the faster neonatal ciliary beat frequency.

Buchdahl *et al* presented strong evidence that children with unexplained chronic respiratory disease, in particular those with symptoms starting in the perinatal period, should be investigated for ciliary dyskinesia.[1] In vitro testing of ciliary beat frequency seems to be the best screening test for ciliary abnormality in this age group. Our results show that it is not possible to extrapolate results of adult ciliary function studies to the neonatal period, however, which confirms the need for separate laboratories to establish their own reference ranges for ciliary beat frequencies at various ages.

We would like to thank Nottingham Hospital trustees for financial help.

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CURRENT TOPIC

Surfactant treatment for premature babies—a review of clinical trials

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In the late 1950s it was shown that respiratory distress syndrome was associated with a deficiency of pulmonary surfactant.[1] In the last 10 years several different preparations of surfactant have now been the subject of randomised controlled trials.

Surfactants

Surfactant TA, developed in Japan (Tokyo-Tanabe), is extracted from homogenised cow lungs.[2–6] To achieve optimum physical properties, dipalmitoylphosphatidylcholine, palmitic acid, and triglyceride are added. It contains 48% dipalmitoylphosphatidylcholine, 16% unsaturated phosphatidylcholine, 4% phosphatidylglycerol, 4% triglyceride, 8% fatty acids, 7% cholesterol, sphingomyelin, and other lipids and 1% apoproteins SpB and SpC. It is freeze dried and when used 100–200 mg is sonicated for five minutes with 3–4 ml saline.

The Japanese surfactant, modified by Abbott laboratories, is called *Survanta*.[7–9] It is a frozen aqueous suspension of 25 mg/ml and contains approximately 88–90% phospholipids (of which 50% is disaturated phosphatidylcholine), 3% triglycerides, 6% free fatty acids, 1% protein, and 0·2% cholesterol. It is thawed before use in a dose of 4 ml/kg.

Calf lung surfactant (CLSE) is made by extracting surfactant from calf lungs.[10–13] It contains 90–97% phospholipid of which 85% is phosphatidylcholine (70% disaturated), 6% phosphatidylglycerol, 4% phosphatidylinositol, 3% phosphatidylethanolamine, 1% sphingomyelin, and 5% cholesterol and cholesterol esters, and 1% protein which is mainly low molecular weight apoproteins SpB and SpC. It is sterilised by flash autoclaving. Before use 90 mg are vortexed with 3 ml of saline.

Porcine surfactant (Curosurf, Chiesi) is extracted from minced pig lungs.[14–16] It consists of 99% lipids and 1% hydrophobic proteins with a molecular weight less than 15 kDa. It is used as a suspension of 80 mg/ml at 200 mg/kg.

Bovine surfactant (SF–RI 1; renamed Alveofact, Thomae) is extracted from cow lung lavage, containing 99% phospholipids and neutral lipids and 1% surfactant associated, proteins SpB and SpC.[17] It is used in a suspension of 45 mg/ml.

Human surfactant is extracted from amniotic fluid.[18–20] It contains apoproteins SpA, SpB, and SpC. It is used as 60 mg/kg suspended saline.

In Belfast an artificial surfactant was made from dipalmitoylphosphatidylcholine (1 g), high density lipoprotein (4 ml), and saline, sterilised by irradiation, sonicated just before use, and given as a 3–5 ml dose into the endotracheal tube at birth.[21] This is no longer used.

Artificial lung expanding compound (ALEC, Pumactant, Britannia Pharmaceuticals) is made from dipalmitoylphosphatidylcholine and unsaturated phosphatidylglycerol in a w:w ratio of 7:3 and contains no protein.[22–30] It has been used as a powder and as a suspension of 50 to 100 mg in 1 ml cold saline.

Exosurf (Wellcome) contains dipalmitoylphosphatidylcholine 108 mg, tyloxapol 8 mg, and hexadecanol 12 mg in 10 ml saline without protein.[31] It is used as 5 ml/kg instilled into the endotracheal tube. Although preliminary results have been presented, there are no published reports of clinical trials.

Clinical trials

There are now at least 15 peer reviewed papers of controlled clinical trials. There are eight trials of surfactant given at birth called 'prophylactic treatment' and seven trials of surfactant given when babies with respiratory distress syndrome required ventilation, called 'rescue treatment'. The basic data about the trials are shown in tables 1 and 2.

Comparing the prophylactic and rescue trials is not satisfactory. Not least because the rescue trials enrol only seriously ill babies and the prophylactic trials include all babies at risk of developing respiratory distress syndrome. Comparisons between trials within prophylactic or rescue groups are difficult because the entry criteria were different. For example, in the prophylactic trials, some randomised all babies born below 35 weeks' gestation, and others enrolled only babies between 25 and 29 weeks' gestation. Some trials retrospectively excluded babies who had mature lecithin:sphingomyelin ratios; others included babies regardless of their lung maturity. In the rescue trials some enrolled babies receiving at least 60% oxygen, and others enrolled babies receiving more than 40% oxygen. Some trials entered all babies even if they were compromised by asphyxia, haemorrhage, infection, or very prolonged rupture of

Table 1 Basic data for the prophylactic trials

Author	*Surfactant*	*Dose (mg)*	*Volume (ml)*	*Placebo*	*Control (n)*	*Surfactant (n)*	*Inclusion criteria (weeks' gestation)*	*Exclusion criteria*	*Retreatment*
Enhorning *et al*[10]	CLSE	75–100	3–4	None	33	39	<30	Acute deliveries	No
Kendig *et al*[13]	CLSE	90	3	Saline	31	34	25–29	Non-intubated babies	No
Kwong *et al*[11]	CLSE	90	3	Saline	13	14	24–28	Congenital malforations, steroids	No
Merritt *et al*[19]	Human	60	3	Air	29	31	24–29	Congenital malformations, L:S>1·9, PG-ve	Yes
Halliday *et al*[21]	DPPC/HDL	30	3–5	None	51	49	25–33	Congenital malformations, L:S>1·9	No
Morley *et al*[24 25]	ALEC	25	Powder	None	75	54	<34	Congenital malformations	No
Morley *et al*[25 26]	ALEC	50–100	1	Saline	171	170	23–34	Congenital malformations	Yes
Ten centre[27]	ALEC	100	1	Saline	149	159	25–29	Congenital malformations,	Yes

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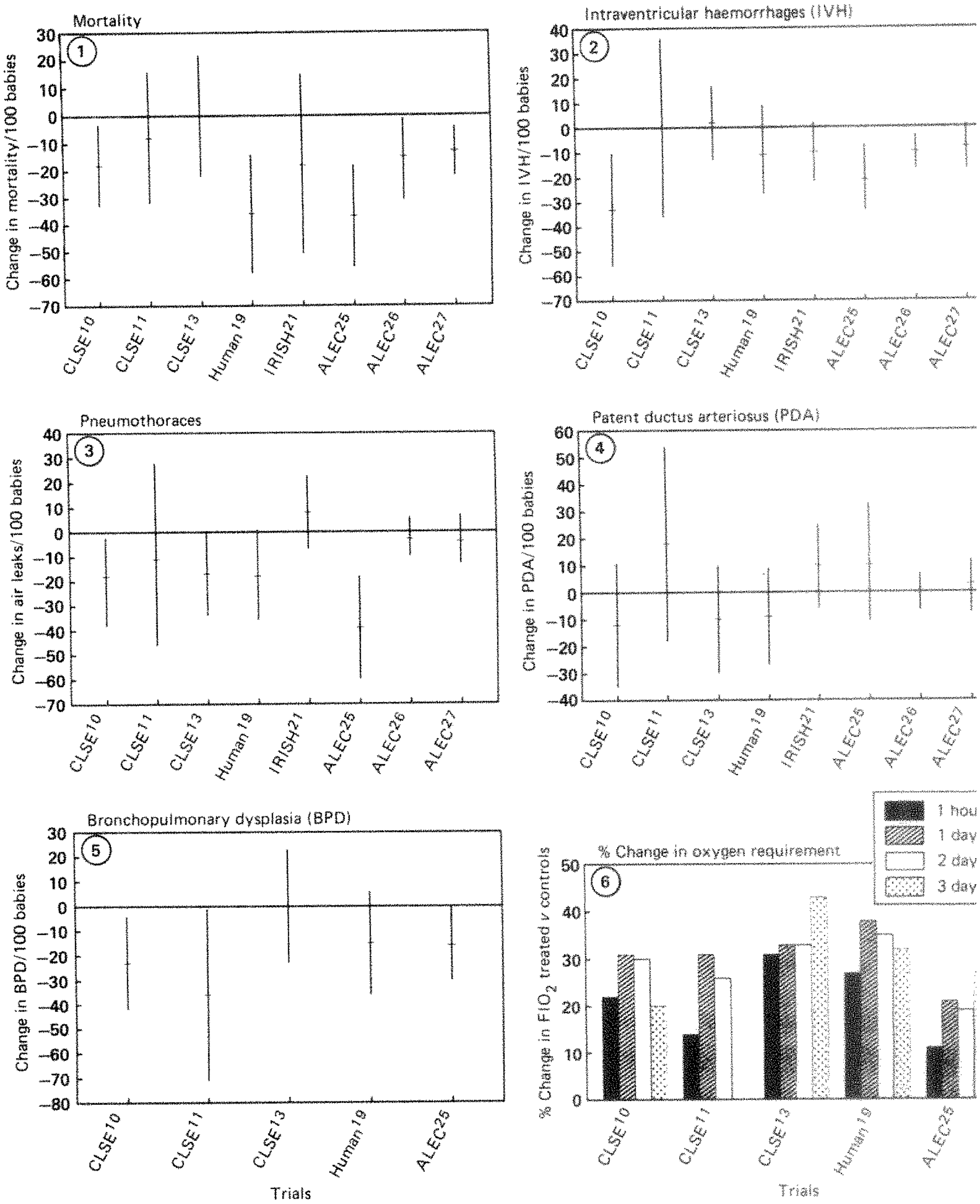

Figures 1–6 Prophylactic trials. Bars are 95% confidence intervals for difference in incidence between treated and control groups. CLSE, calf lung surfactant; ALEC, artificial lung expanding compound.

rescue trials. In the rescue trials confidence intervals are wide because of small numbers. Only the trial of Raju *et al* of sufactant TA[6] and the trial of Curosurf[16] demonstrated significant reductions in mortality. In the prophylactic trials, there were significant reductions in mortality with one trial of CLSE,[10] but not in the other two, human surfactant,[19] ALEC powder,[25] and ALEC suspension.[26 27] Overall surfactant treatment approximately halved the

trials reported the percentage of babies grade 3 or 4 haemorrhages these are sented otherwise the numbers represent total number of intraventricular haemorrha Although the trial of McCord *et al* Curosurf[15] showed a significant reduction was a subgroup from the European Curo trial,[16] which showed no effect on intraventri lar haemorrhage, even grade 3 and 4. Surv showed no effect in the American trial[7] b

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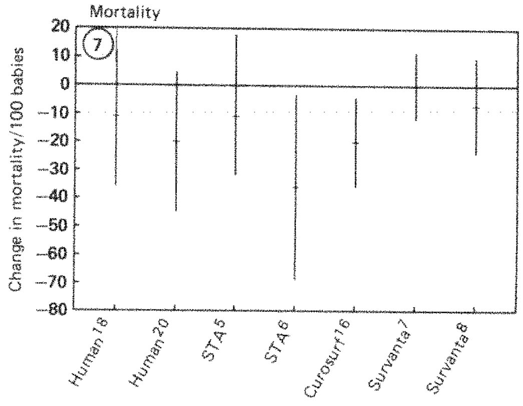
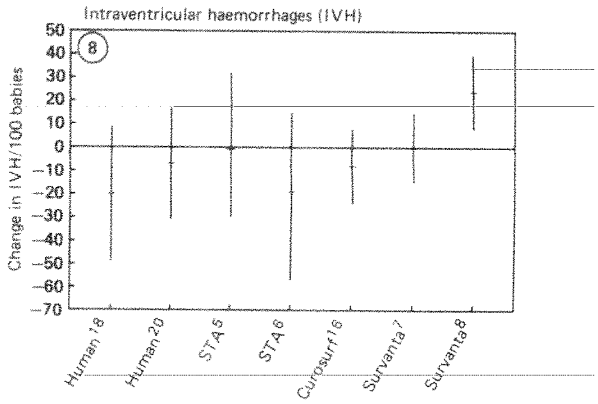
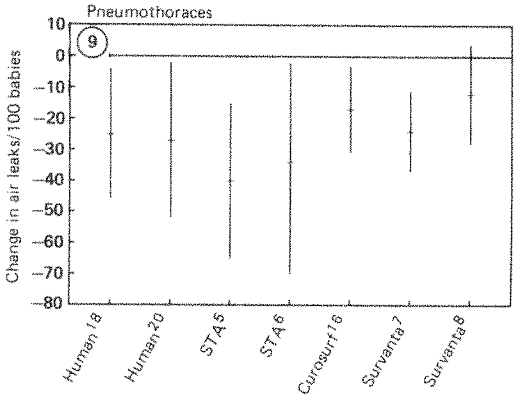
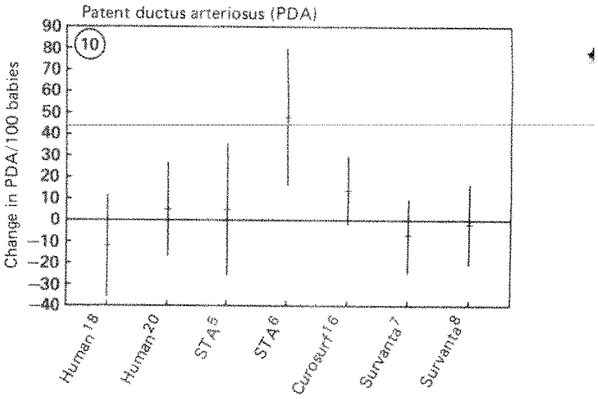
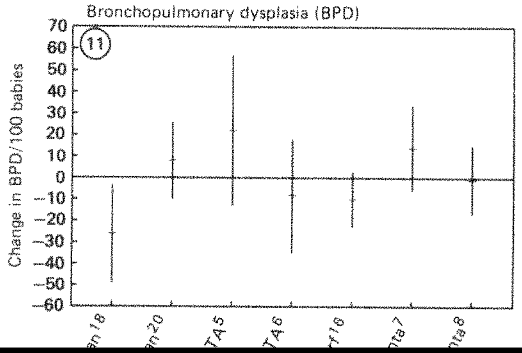
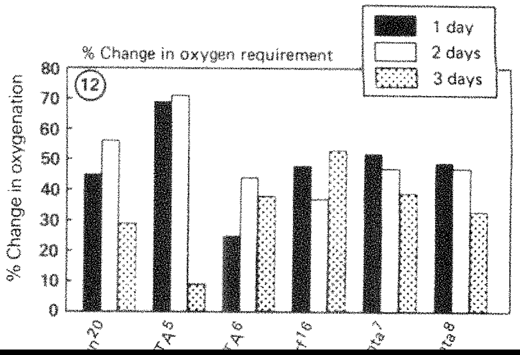

Mortality
7
Change in mortality/100 babies
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
Human 18
Human 20
STA 5
STA 6
Curosurf 16
Survanta 7
Survanta 8


Intraventricular haemorrhages (IVH)
8
Change in IVH/100 babies
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
Human 18
Human 20
STA 5
STA 6
Curosurf 16
Survanta 7
Survanta 8


Pneumothoraces
9
Change in air leaks/100 babies
10
0
−10
−20
−30
−40
−50
−60
−70
−80
Human 18
Human 20
STA 5
STA 6
Curosurf 16
Survanta 7
Survanta 8


Patent ductus arteriosus (PDA)
10
Change in PDA/100 babies
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
−40
Human 18
Human 20
STA 5
STA 6
Curosurf 16
Survanta 7
Survanta 8


Bronchopulmonary dysplasia (BPD)
11
Change in BPD/100 babies
70
60
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
an 18
an 20
TA 5
TA 6
rf 16
nta 7
nta 8


1 day
2 days
3 days
% Change in oxygen requirement
12
% Change in oxygenation
80
70
60
50
40
30
20
10
0
n 20
TA 5
TA 6
rf 16
nta 7
nta 8

[redacted]

percentage improvement caused by the surfactant treatment. Although surfactant treatment improves oxygenation the effect is only demonstrable in most of the trials during the first few days with little effect over seven days. All rescue trials show a significant reduction in oxygen requirement. In the five prophylactic trials where this data is presented there is also a reduction in oxygen requirements.

TIME IN OXYGEN AND RECEIVING VENTILATION

With more survivors surfactant treatment could result in babies receiving respiratory support for a longer time. Not all the trials give the length of time babies received oxygen. In the trial of Gitlin *et al* of Surfactant TA there was a significant reduction in time receiving oxygen but not in the time to extubation.[5] Whereas in the trial of Raju *et al* with Surfactant TA there were no signifcant differences.[6] In the trial of Curosurf there was no significant difference in the duration of artificial ventilation.[16] In the 10 centre trial of ALEC there was a significant reduction in the hours of ventilation and hours in more than 30% oxygen for survivors at 10 days. In the high dose/low dose randomised trial of Surfactant TA significantly fewer of the babies receiving the high dose were ventilated for 30 days or more.[3]

CHANGES IN AIRWAY PRESSURE

Not all trials show changes in ventilator pressure. They have shown a consistent improvement during the first three days with a reduction in mean airway pressure of between 2 and 5 cm H_2O. Taking account of the numbers of babies and severity of disease in the different trials there is no significant difference in the effect of different surfactants.

CHANGES IN COMPLIANCE OF THE RESPIRATORY SYSTEM

Both natural surfactant and artificial surfactants can improve thoracic compliance of premature animals.[30 31] ALEC improves the compliance of the respiratory system in babies less than 30 weeks' gestation from 0·54 to 0·91 ml/cm H_2O/kg ($p<0·05$) by six hours after prophylactic treatment.[29] This is not apparent in babies of 30 weeks or more. Couser *et al* in a prophylactic trial of Survanta measured dynamic compliance during ventilation in unparalysed babies.[9] They showed no difference in the lung compliance, resistance, or tidal volume at one hour after each dose compared with the controls. However, the compliance of the surfactant treated group increased over seven days. In the first 72 hours the compliance of the controls was approximately 0·35 ml/cm H_2O/kg and the surfactant treated approximately 0·55 ml/cm H_2O/kg. By day seven, the controls had a compliance of 0·45 ml/cm H_2O/kg and the surfactant treated 0·85 ml/cm H_2O/kg ($p<0·05$).

VARIATION IN INDIVIDUAL RESPONSE

Despite early beliefs that all babies with respiratory distress syndrome were surfactant deficient and therefore surfactant treatment would cure them, not all babies respond to treatment. Fujiwara and others have reported that with Surfactant TA approximately two thirds had an immediate and sustained response in oxygenation, one sixth relapsed, and one sixth had a poor or no response.[32 33] They thought that the factors leading to an unsatisfactory response were a patent ductus arteriosus, cardiogenic shock or persistent fetal circulation, and air leaks. It is not surprising that these very immature babies, who suffer from so many compounding diseases and complications, should not always respond to surfactant treatment. Perhaps it is more surprising that so many do.

FOLLOW UP

Few follow up studies have been reported. In a group of 235 Cambridge born survivors from a randomised trial of ALEC follow up information was available for 98% at 18 months.[34] There was no difference between ALEC treated and control babies in the incidence of neurological impairment, mental impairment, respiratory infections, allergies, or hospital admissions up to 18 months' post-term. In those born before 30 weeks' gestation (where surfactant most improves survival) the proportion of normal survivors was 57% in the treated group compared with 41% of the controls. Similar results have been reported for other surfactants by Vaucher *et al*[35] and Halliday *et al.*[36] Improved neonatal survival does not appear to be associated with neurodevelopmental handicap.

Conclusion

The overview of all the trials of surfactant treatment shows that it benefits babies less than 30 weeks' gestation. The only major side effect is in the rescue trials where there was an increase in patent ductus arteriosus in babies treated with natural surfactant.

Prophylactic treatment is beneficial and apparently harmless, even though some babies who would not have developed respiratory distress syndrome were treated.

One of the concerns about natural surfactant preparations is the protein to which babies may become sensitised. The evidence to date is that any antibodies which are produced do not appear to cause problems.

Although it has been suggested that artificial surfactant is not as effective as natural surfactant because it does not contain the apoproteins,[37] the results of the trials of artificial surfactant ALEC have shown that it reduces the incidence of neonatal complications and improves the outcome of babies less than 30 weeks' gestation at least as well as natural surfactants.

The evidence suggests that the surfactants most likely to have longer term benefits are CLSE, human surfactant, and ALEC when used prophylactically and Curosurf used in rescue mode. The decision about which surfactant should be used will depend upon its possible side effects, its ease of preparation and delivery, its availability, and its price.

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REGULAR REVIEW

Prenatal diagnosis of enzyme defects—an update

Bryan Winchester, Elisabeth Young

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modified to increase the success rate of these cultures and provided enzyme activities are expressed in these amniocytes, it should be possible to make an earlier diagnosis of those enzymic defects which cannot be made directly on chorionic villi but require culture of cells. It has also been possible to make a diagnosis of I cell disease in a fetus by the demonstration of an increase in lysosomal enzymic activities in amniotic fluid taken at 10–12 weeks' gestation.[14] Work is currently in progress to see if the concentrations and patterns of glycosami-

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mutation because it is uncommon or new. Alternatively, RFLP analysis of DNA from the fetus, affected child, and parents may be informative. It has been predicted that the latter approach can be applied to 90% of white families with phenylketonuria.

Another disorder in which DNA analysis has been used for prenatal diagnosis is Tay-Sachs disease, which results from a deficiency of hexosaminidase A and has an occurrence of 1/3600 in the unscreened population of Ashkenazi Jews. Three mutations in the gene encoding the tion or perhaps in situ hybridisation for X linked disorders. Theoretically, it would be possible to detect specific mutations in an enzyme gene using the polymerase chain reaction or to measure enzymic activity directly in a very small number of isolated fetal cells.

Of related interest is the observed increased activity of some lysosomal enzymes in the serum of pregnant women compared with the activity in the same women when not pregnant—for example, iduronate sulphate sulphatase (the enzyme defective in Hunter's disease). If a fetus is affected with Hunter's disease, however, no increase in this enzyme is found in the maternal serum, whereas with a normal or heterozygous fetus the rise is observed. The origin of this increased activity needs further investigation as does the whole subject of fetal material in the maternal circulation.

Testing of preimplantation embryos

Another way of avoiding the development of a fetus carrying a genetic defect is to diagnose the defect in preimplantation embryos and only transfer unaffected embryos to the uterus.[29] Recently important ethical and practical steps have been taken towards making this a feasible proposition for some genetic defects. The acceptance by the British parliament of a clause in the Human Fertilization and Embryology Bill permitting carefully regulated research on embryos up to 14 days from conception has removed the legal constraint. It is now clear that it is technically possible to remove one or two

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enzymes of clinical relevance, for example, hexosaminidase have also been found to be low at this stage of development.

DNA analysis may be possible for specific human mutations after amplification of the DNA in the blastomere (approximately 6 pg of DNA); β thalassaemia can be diagnosed by amplification of DNA from a single blastomere from a mouse preimplantation embryo.[34]

An exciting new extension of this procedure to unfertilised human oocytes and to the first polar bodies isolated from them offers the possibility of detection of defects before fertilisation, with the benefit of not testing the embryo or fetus at any stage.[35] Preliminary results have shown that it is possible to amplify the DNA sequence containing the sickle cell mutation site from human oocytes and polar bodies. Further work is necessary to show whether both sequences are amplified in a heterozygote.

Fetal treatment of enzymic defects

For a small number of enzyme defects treatment in utero is an alternative to prenatal diagnosis and the option of termination.[36] This may take the form of vitamin supplementation for disorders responsive to additional cofactor, for example, cobalamin E disease, dietary control as in phenylketonuria, or drug administration to suppress a harmful secondary metabolic activity resulting from the primary enzymic defect, for example, the suppression by glucocorticoid of adrenal production of adrenogenic steroids in adrenal hyperplasia (due to a defiof fetal liver.[42] Two disorders where the methodology for prenatal diagnosis would appear to be available are the defect of mitochondrial fatty acid β oxidation due to a deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase[43] and atypical phenylketonuria due to a deficiency of glutamyl transpeptidase cyclohydrolase I (McKusick No 23391).[44]

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Dr Charles West (1816–98) of London and the cold syndrome

P M Dunn

Charles West was born in London, the son of a Baptist lay preacher. He was educated at a school run by his father and then apprenticed to a general practitioner in Amersham. In 1833 he entered St Bartholomew's Hospital and after studies there and in Bonn and Paris, took his MD in Berlin in 1837. After a short period of general practice in London he visited Dublin where he made a special study of midwifery. Returning to London he was appointed physician to the Royal Universal Dispensary for Women and Children, Lambeth, in 1842 and lecturer in midwifery at the Middlesex Hospital in 1845, and later also at St Bartholomew's Hospital (1848–61). His *Lectures on Diseases of Infancy and Childhood*, published in 1848, were a great success, passing through seven editions in Great Britain, five in America, and transla-

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too, the premonitory loss of temperature may be perceived in weakly children without being succeeded by the appearance of spots of induration. This, however, is exceptional, and in the majority of instances the sinking of the temperature and the extension of the induration advance together, and the warmth of the surface may eventually fall from 100° to 90°, 80°, or even lower. If the induration become very extensive, it affects the integuments of the chest and the abdomen, as well as the extremities, and the body feels cold and stiff, as though it were frozen.

This condition is, as might be expected, attended with great impairment of the general health, and with a very remarkable degree of emaciation. Children suffering from it are extremely weak, often too weak to suck: their pulse is very small, their respiration abdominal, and their cry is faint and whimpering, wholly unlike that of a healthy infant. In some of the worst cases, too, a bloody fluid is discharged in considerable quantity from the nose and mouth. If the indurated parts be punctured, a small quantity of reddish serum escapes from them, though generally without much diminution of their previous hardness.

If the induration be at all general, death almost invariably takes place; and so great is the fatality of the affection, that, including even

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panded condition of the lung; and we can understand how it may happen, if children be exposed to cold immediately after birth, and then transferred to the ill-ventilated wards of a foundling hospital, and there fed with food far other than that which nature destined for them, that respiration may be but very imperfectly established; that their temperature may consequently fall, and the blood flowing in part through the unclosed foetal passages may stagnate in its course, may give rise to passive effusions into the great cavities of the body, and to an anasarcous swelling of the surface. There are, it is true, some peculiarities in this form of oedema, but not such as to invalidate the above explanation of the cause to which it is due.

The *treatment* of this affection implies the removal of every cause likely to induce it. Hence warmth stands foremost both as a curative and as a preventive measure. The warm bath may be resorted to as a means of raising the child's surface to a proper temperature, provided its extreme weakness do not contra-indicate that measure. Gentle friction with warm oil is a means which has been tried for this purpose with advantage. The child should be nourished with breast-milk, even if it be too feeble to suck, and stimulants, of which white-wine whey is a very good one, will in many instances be needed. Defective respiration being

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